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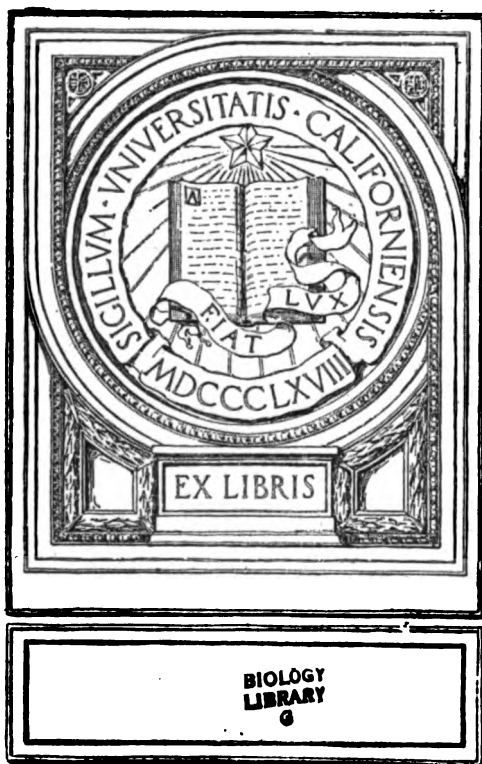
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No. 1

NATURE AND QUANTITATIVE DETERMINATION OF THE REDUCING SUBSTANCE IN NORMAL AND PATHOLOGIC CEREBROSPINAL FLUID*

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NEW YORK

I. INTRODUCTION

During the past year we have had opportunity to make a series of quantitative determinations of the reducing power of various specimens of normal and pathologic cerebrospinal fluid, and also to carry out certain observations concerning the nature of the reducing substance. The data thus derived serve as the basis of this communication.

II. THE NATURE OF THE REDUCING SUBSTANCE

It is generally assumed that the reducing agent in cerebrospinal fluid is dextrose—the sugar of blood and body fluids. A review of the literature, however, discloses that there has been considerable divergence of opinion. Halliburton,¹ whose views are quoted in several current textbooks, concluded that the reducing substance was pyrocatechin or a pyrocatechin derivative. Connall² states that it is galactose, although he gives no references or experimental data to uphold this view. The observations of Nawratski,³ Zdarek,⁴ Rossi⁵ and others, however, indicate that the reducing agent is a fermentable, dextrorotatory sugar, presumably dextrose.

*From the Children's Wards and the Pathological Laboratory, Bellevue Hospital, New York.

*Read at the meeting of the American Pediatric Society, Lakewood, N. J., May, 1915.

1. Halliburton: Text Book of Chemical Physiology and Pathology, London, 1891. Thompson, Hill and Halliburton: Observations on the Cerebrospinal Fluid in the Human Subject, Trans. Path. Soc., London, 1899, liv, 344.

2. Connall: A Study of the Cerebrospinal Fluid in the Infective Diseases of the Meninges with Special Reference to Cerebrospinal Fever, Quart. Jour. Med., 1909, iii, 152.

3. Nawratski: Zur Kenntniss der Cerebrospinalflüssigkeit, Ztschr. f. physiol. Chem., 1897, xxiii, 533.

4. Zdarek: Ein Beitrag zur Kenntniss der Cerebrospinalflüssigkeit, Ztschr. f. physiol. Chem., 1902, xxxv, 211.

5. Rossi: Sulla natura della sostanza reducente contenuta nel liquido cefalo-rachidea, Clin. med. ital., 1899, xxxviii, 422.

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In order to obtain additional evidence on this subject we made the following experiments:

Mixed specimens of practically normal⁶ cerebrospinal fluid, from 460 to 700 c.c. each, were precipitated with absolute alcohol, filtered and evaporated at a low temperature in slightly acid solution to a volume of 30 c.c. The resulting solution was filtered and subjected to tests, the results of which may be summarized as follows:⁷

1. Quantitative determination of the reducing substance as dextrose by Benedict's solution gave percentages of 0.86 to 1.3.
2. The solutions were dextrorotatory and the rotation corresponded to a percentage of dextrose nearly identical with that obtained by Benedict's reagent.⁸
3. The solutions were fermented by yeast with the production of alcohol and carbon dioxid. The mixture was acid in reaction (litmus).
4. A crystallin osazone was obtained which was insoluble in hot water, soluble in alcohol and pyridin and melted at 200 to 208 C.
5. A repetition of the procedure of Halliburton gave no precipitate of pyrocatechin.

It has been found by a number of observers that the reducing substance in cerebrospinal fluid is destroyed by bacterial growth in twenty-four to seventy-two hours. We were able to confirm this observation on a number of occasions. It therefore seemed only rational to assume that if the reducing action of cerebrospinal fluid were due to pyrocatechin, the reducing power of this substance should be destroyed by bacterial growth. With this idea in mind the following experiment was made:

Pyrocatechin was dissolved in nutrient broth in sufficient quantity to give a reducing action equal to normal cerebrospinal fluid. This reducing power was not appreciably decreased by bacterial growth.

The observations cited indicate that there is no basis for the belief that the reducing substance in normal cerebrospinal fluid is pyrocatechin. Moreover, our results indicate that this agent is a monosaccharid, probably dextrose.

III. QUANTITATIVE DETERMINATIONS OF THE REDUCING AGENT IN CEREBROSPINAL FLUID

But few determinations of the reducing agent in cerebrospinal fluid have been made and these concerned normal or nearly normal

6. Part of the fluid in one specimen was from a patient affected with hydrocephalus, and from one with tuberculous meningitis, but both specimens of fluid contained a normal amount of the reducing substance.

7. These experiments were made on three separate collections of material.

8. The exact results were as follows:

Specimen	Dextrose P. C. Benedict's Solution	Dextrose P. C. Polarimeter
1	0.86	0.77
2	0.97	1.2
3	1.3	1.12

material. Owing to the small amount of this substance usually present, a number of the estimations were made on mixed specimens of fluid obtained from several patients and therefore give no idea of the normal fluctuations. So far as we can ascertain, there have been no quantitative determinations of the reducing power of cerebrospinal fluid in meningeal diseases.

TECHNIC

By means of the method of Lewis and Benedict⁹ for the quantitative determination of blood sugar we were able to make accurate determinations of the reducing power of cerebrospinal fluid by using quantities of 5 c.c. or even less.¹⁰ During the course of the work qualitative tests for comparison were made with Benedict's and Fehling's solutions. We found the reagent of Benedict the more satisfactory, and after experiment adopted the following procedure. To exactly 5 c.c. of the reagent were added 12 drops of cerebrospinal fluid. The mixture was kept at boiling temperature for one to two minutes and allowed to cool spontaneously. The test was usually positive when the fluid contained 0.05 per cent. or more of dextrose.

The Sugar Content of Normal Cerebrospinal Fluid.—The results for normal fluids were obtained from a study of material from forty-five infants and children (Table 1) on whom lumbar puncture was done as a diagnostic procedure. There were a number of cases of meningism, but all fluids showed a normal cell count and no increase of globulin (Kaplan, Noguchi). The maximum amount of sugar found in normal cerebrospinal fluid was 0.139 per cent., the minimum 0.054 per cent. As shown in the table, the amount of sugar contained in the different fluids varied greatly. The cause of this variation is not apparent, but it seems probable that the amount of sugar in each individual may vary from time to time, as is true of blood sugar. Owing to the method of obtaining cerebrospinal fluid, it is impossible to determine the possible influence of diet and other factors, which we know are capable of changing the sugar content of the blood. It is of great interest that the normal variation in the amount of sugar in cerebrospinal fluid is very close to that which obtains for blood. It therefore seemed of interest to ascertain whether there is any correspondence between the blood sugar and the cerebrospinal fluid sugar in the individual case. Accordingly, in ten cases we have made sugar determinations on blood and cerebrospinal fluid which

9. Lewis and Benedict: A Method for the Estimation of Sugar in Small Quantities of Blood, *Jour. Biol. Chem.*, 1915, xx, 61.

10. Five cubic centimeters of cerebrospinal fluid was delivered into a 25 c.c. volumetric flask from an Ostwald-Folin pipet; 10 c.c. of a saturated aqueous solution of picric acid were added; the mixture made up to 25 c.c. with water and filtered. Aliquots of 8 c.c. were used and to each was added 2 c.c. of the aqueous picric solution. Otherwise the method corresponds to the description of Lewis and Benedict.

TABLE 1.—THE PERCENTAGE OF DEXTROSE IN NORMAL CEREBROSPINAL FLUID

No.	Diagnosis	General Characteristics	Per Cent. Dextrose
1	Lobar pneumonia, otitis media	Clear; no increase of pressure; no globulin; no cells	0.0756
2	Acute tonsillitis, meningism	Clear; no cells; no globulin; pressure moderately increased	0.09
3	Congenital deformity, lobar pneumonia	Normal	0.1390
4	Tuberculosis of spinal column	Normal	0.08
5	Normal	0.065
6	Convulsions	Normal	0.08
7	Normal	0.0992
8	Tuberculous bronchopneumonia, otitis media, rickets	Normal	0.0692
9	Normal	0.0674
10	Bronchopneumonia	Normal	0.0348 *
11	Septicemia	Normal	0.094
12	Malnutrition, meningism	Normal	0.056
13	Lobar pneumonia	Normal	0.075
14	Gastro-enteritis, bronchopneumonia; meningism	Normal	0.059
15	Myelogenous leukemia	Normal	0.118
16	Toxic psychosis	Normal	0.062
17	Normal	0.0692
18	Malnutrition	Normal	0.0692
19	Tuberculous bronchopneumonia	Normal	0.08
20	Rickets	Normal	0.071
21	Gastro-enteritis, meningism	Normal	0.0134 *
22	Pneumonia, meningism	Pressure increased; otherwise normal	0.0674
23	Lobar pneumonia	Normal	0.088
24	Acute otitis media, pneumonia	Normal	0.0692
25	Empyema	Normal	0.134
26	Malnutrition	Normal	0.065
27	Malnutrition	Normal	0.0786
28	Otitis media, meningism	Normal; 18 cells	0.064
29	Otitis media, meningism, pneumonia	No globulin; 11 cells; pressure much increased	0.0818
30	Pneumonia, acute parenchymatous, nephritis	Normal pressure +	0.0196 *
31	Acute gastro-enteritis, meningism	Normal pressure +	0.0592
32	Rickets, internal hydrocephalus	Normal	0.0588
33	Acute otitis media, meningism	Normal	0.075
34	Convulsions	Normal	0.066
35	Gastro-enteric intoxication, meningism	Pressure +; otherwise normal	0.1390 *
36	Cretinism, lobar pneumonia	Normal	0.0786
37	Normal	0.063
38	0.057
39	Malnutrition	Normal	0.1042

TABLE 1.—(Continued)

No.	Diagnosis	General Characteristics	Per Cent. Dextrose
40	Gonococcus, vaginitis	Pressure +; otherwise normal	0.066
41	Pertussis, meningism	Pressure +; otherwise normal	0.064
42	Septicaemia	Normal	0.091
43	Tetany	Normal	0.066
44	Pneumonia, meningism	Normal	0.085
45	Convulsions	Pressure +; otherwise normal	0.0486
46	Epilepsy	Normal	0.065
47	Rheumatic fever	Normal	0.094
48	Normal	0.0836
49	Bronchopneumonia	Normal	0.1042

* Moribund.

TABLE 2.—SUGAR CONTENT OF CEREBROSPINAL FLUID IN EPIDEMIC CEREBROSPINAL MENINGITIS

No.	Age Years	Dextrose Per Cent.	Remarks
1	11	* 0.09 0.08 0.0868 0.0818	Ill two days. Delirious. Second specimen. Following day intraspinal injections of antimeningococcic serum. Following day improvement. Great improvement.
2	$\frac{1}{8}$	0.0134 0.0134 0.0134	Following day worse. Death.
3	$\frac{1}{8}$	* *	Condition poor. Seven hours later treated with serum. Recovery. Other specimens not obtained.
4	$5\frac{1}{2}$	* 0.036 0.0459 0.051	Very ill. Treated with serum. Following day. Following day. Fourth day. Great improvement. Recovery.
5	$3\frac{1}{2}$	* 0.0459 0.059	Moderately ill. Serum treatment. Improvement. Very much better. Recovery.
6	0.075 0.058 0.062	Very ill. Serum treatment. Following day improved. Much better. Ultimate recovery.
7	0.027 0.065 0.04	Very ill. Serum. Condition worse. Following day. Much worse. Death.
8	* 0.0362 0.05 0.057	Very ill. No apparent improvement. Following day. Two days later. Much improved. Two days later. Much better. Recovery.

* Too small to determine.

TABLE 3.—SUGAR CONTENT OF CEREBROSPINAL FLUID IN TUBERCULOUS MENINGITIS

No.	Age Years	Dextrose Per Cent.	Remarks
1	7	0.035 0.0324 0.0674	Two days later. Three days later. Tubercle bacilli in spinal fluid.
2	2½	0.0674 0.0318	Autopsy. General miliary tuberculosis. Tubercle bacilli in cerebrospinal fluid.
3	9		Autopsy. General miliary tuberculosis.
4	4	0.0454	X-Ray. General miliary tuberculosis.
5	4	0.0314 0.0338 0.0334	Two days later. Four days later. Tubercle bacilli in cerebrospinal fluid.
6	11	0.0294	Tubercle bacilli in cerebrospinal fluid.
7	1½½	0.0330 0.0380	Autopsy. General miliary tuberculosis. First specimen. Second specimen. Tubercle bacilli in cerebrospinal fluid.
8	2½	0.056 0.0464	First specimen. Second specimen. Tubercle bacilli in cerebrospinal fluid.
9	5½	* * 0.0370 *	First specimen. Second specimen. Third specimen. Fourth specimen.
10	1½½	0.039 0.022	First specimen. Second specimen. Tubercle bacilli in cerebrospinal fluid.
11	5½	0.0718	Tubercle bacilli in cerebrospinal fluid.
12	4	0.022 * 0.0426 0.0402 0.0318 0.0298 0.03518	First specimen. Tubercle bacilli in cerebrospinal fluid. Second specimen. Tubercle bacilli in fluid. First specimen. Second specimen. Third specimen. Fourth specimen. Tubercle bacilli in cerebrospinal fluid.
13	3	0.0426	Tubercle bacilli in fluid.
14	8	0.0402 0.0318 0.0298 0.03518	First specimen. Second specimen. Third specimen. Fourth specimen. Tubercle bacilli in cerebrospinal fluid.
15	2	0.0351 *	First specimen. Tubercle bacilli in fluid. Second specimen.
16	3½	0.0466 0.0464	First specimen. Tubercle bacilli in fluid. Second specimen.
17	8	*	Tubercle bacilli in fluid.
18	1½	0.038 0.0240	First specimen. Tubercle bacilli in fluid. Second specimen.
19	1½	0.069	Tubercle bacilli in fluid.
20	5	0.059 0.08 0.0588 0.0674 0.0606	First specimen. Second specimen. Third specimen. Fourth specimen. Sixth specimen. Tubercle bacilli in cerebrospinal fluid.
21	4	0.0422 0.0181	First specimen. Second specimen. Autopsy. General miliary tuberculosis.
22	¾	0.0422 0.0261	First specimen. Second specimen.
23	11	0.027 0.0324	First specimen. Tubercle bacilli in fluid. Second specimen.

* Too small to determine.

were obtained at the same time. In only two instances were the values similar. These results indicate that although the variations in the blood sugar and the cerebrospinal fluid sugar are practically identical yet there is no correspondence in the individual case at a given time.

TABLE 4.—CEREBROSPINAL MENINGITIS, MISCELLANEOUS TYPES

No.	Age Years	Disease	Dextrose Per Cent.	Remarks
1	1½	Pneumococcus meningitis	0.037	Five days' duration.
2	½	Influenza meningitis	*	First specimen.
			0.0214	Second specimen.
			0.022	Third specimen.
3	Influenza meningitis	*	Moribund on admission
4	5½	Pneumococcus meningitis	0.0174	First specimen.
			*	Second specimen.
5	9	Streptococcus meningitis	0.0992	First specimen; fluid shows no cell or globulin increase.
			0.0718	Second specimen; seven cells per cubic mm.; no globulin.
			0.064	Third specimen; 156 cells; marked increase in globulin.
			0.0232	Fourth specimen; fluid cloudy; many pus cells.

* Too small to determine.

TABLE 5.—SUGAR CONTENT OF CEREBROSPINAL FLUID IN POLIOMYELITIS AND POLIO-ENCEPHALITIS

No.	Age Years	Dextrose Per Cent.	Remarks
1	5½	0.063	Subacute stage. Anterior poliomyelitis.
2	5	0.0588	First specimen. Acute stage poliomyelitis.
		0.065	Second specimen.
3	0.088	Chronic stage. Duration two weeks.
4	0.0376	Acute polio-encephalitis. First specimen; 830 cells.
		0.0426	Second specimen; 750 cells.
		0.0398	Third specimen.
		0.0394	Fourth specimen; 170 cells.
		0.0395	Fifth specimen.
		0.044	Sixth specimen; 40 cells.

Of interest are the results from four patients who were moribund at the time of examination. In three instances the dextrose value was very low; in one it was high.¹¹

The Sugar Content of Cerebrospinal Fluid in Cases of Epidemic Cerebrospinal Meningitis.—Eight cases of meningococcic meningitis were observed and are described in Table 2. In common with the results of Connall, DuBois¹² and others we found that the reducing agent is usually greatly decreased. Connall states that the reducing power usually increases with improvement of the patient. This is well shown in Cases 1, 4, 5 and 8. In Case 6, however, there was a normal sugar value at the height of the disease and no increase with improvement. Patient 7 showed an increase in the reducing action of the cerebrospinal fluid despite the fact that he became progressively worse.

TABLE 6.—SUGAR CONTENT OF CEREBROSPINAL FLUID IN CEREBROSPINAL SYPHILIS

No.	Age Years	Dextrose Per Cent.	Remarks
1	0.060	Case 3, Table 7, Wassermann positive on blood and cerebrospinal fluid. Idiocy.
2	0.059 0.0558 0.0592 0.0514	Hydrocephalus. First specimen. Second specimen. Third specimen. Fourth specimen.

The Sugar Content of Cerebrospinal Fluid in Cases of Tuberculous Meningitis.—A number of observations have been published concerning qualitative tests of the reducing power of cerebrospinal fluid in cases of tuberculous meningitis. The results are inconstant, but in a large percentage of the cases the fluid was capable of reducing copper salts (Connall, DuBois and others). In consideration of these results, our quantitative determinations are of special interest. (Table 3.) We found that in a single specimen of spinal fluid the dextrose percentage may be normal, slightly reduced or greatly reduced and this variation could be traced to no definite influence. In most of our cases, however, there was a decrease in the sugar value at some stage of the disease and usually as the disease progressed. To this there were only two marked exceptions. In Case 1 the sugar was decreased at the time of the first tap but at the time of the third

11. These cases are cited in Table 1, but can scarcely be considered normal.

12. Du Bois: Summary of Four Years of Clinical and Bacteriological Experience with Meningitis in New York City, *AM. JOUR. DIS. CHILD.*, 1915, ix, 1.

was normal. In Case 20 the sugar was normal during the entire course of the disease.

Miscellaneous Types of Meningitis.—Cerebrospinal fluid from two cases of pneumococcus meningitis, two cases of influenza meningitis and one of streptococcic meningitis were examined. In all the reducing power was greatly decreased or absent. Case 5 is of sufficient interest to cite. The patient, a boy of 8 years, was affected with septicemia due to streptococcus pyogenes. The first specimen of cerebrospinal fluid was normal in cell content, globulin and sugar. The patient gradually developed symptoms of meningitis and with their progression the sugar content of the cerebrospinal fluid became less, and at the time when the symptoms were marked, was greatly reduced.

TABLE 7.—SUGAR CONTENT OF CEREBROSPINAL FLUID IN CASES OF IDIOCY

No.	Age Years	Dextrose Per Cent.	Remarks
1	4	0.10	Idiocy and congenital syphilis.
2	0.0692	Idiocy. Epilepsy.
3	11	0.061	Case 1, Table 6. Idiocy; syphilis.
		0.06	Second specimen.
		0.075	Third specimen.
4	0.0514	Wassermann on blood positive; spinal
5	0.066	fluid negative.
6	0.064	Idiocy; spastic paraplegia.

Poliomyelitis and Polio-Encephalitis.—In three cases of poliomyelitis the reducing power of the cerebrospinal fluid was normal. In one case of polio-encephalitis the sugar was decreased.

Idiocy. Congenital Syphilis.—Two cases of cerebrospinal syphilis and six cases of various types of idiocy were observed. In all the sugar content of the cerebrospinal fluid was within the limits of normal.

IV. SUMMARY

1. The reducing substance in cerebrospinal fluid is a fermentable, dextrorotatory sugar, probably dextrose.

2. In infants and children free from meningeal disease the cerebrospinal fluid sugar ranges from 0.05 to 0.134 per cent. (dextrose), approximately the same figures which obtain for blood sugar.

3. There is no decrease in the reducing power of the cerebrospinal fluid in meningism.

4. A large proportion of the cases of tuberculous meningitis show a decrease in the sugar content of the cerebrospinal fluid at some stage of the disease. In a few cases, however, the sugar is normal at all times or diminished but slightly. A decrease only is of diagnostic value.

Our material was obtained from the service of Dr. L. E. La Fétra at Bellevue Hospital. We desire to express our indebtedness for this privilege and for encouragement in the work. To Dr. Charles Norris, Director of the Pathological Laboratory, we are indebted for his kindness in placing the facilities of his laboratory at our disposal.

FAMILIAL SYPHILIS*

P. C. JEANS, M.D.

ST. LOUIS

During the past few years at the St. Louis Children's Hospital it has been our custom to follow all cases of syphilis coming for treatment, and in addition to investigate the remainder of each patient's family in regard to the occurrence of syphilitic infection. In this paper some of the results of this familial study are given. There has been no selection of cases or families, other than that those records have been analyzed in cases in which the investigation was more or less complete.

Except in three instances of second marriages, and possibly one other, in the 100 families studied, the father was apparently the first infected. In the three second marriages the mother was apparently infected by her first husband.

SYPHILIS IN THE MOTHERS OF SYPHILITIC CHILDREN

Whether or not the mother of a syphilitic child is necessarily infected has been a much disputed point. In the families studied in addition to the history, Wassermann reactions were made on eighty-five mothers of syphilitic children. These were positive in seventy-three instances (85.9 per cent.) while twelve mothers gave a negative Wassermann reaction. Of the twelve mothers who gave negative Wassermann reactions the interval between the birth of their last child with positive reaction and the examination was two months, five months, nine months, three years, four years, seven years, seven years, ten years, twelve years, thirteen years, thirteen years and thirteen years. The mother examined at two months' interval had evidence of active syphilis at the time of examination; so strong that the result of the Wassermann was doubted. She also gave a history of a primary lesion one year previously, with treatment. The one at five months also gave a positive history of infection. The one at nine months had been under a physician's care for some time before being examined by us and may have had treatment. She states that blood tests were made and medicine given. The one at three years was accidentally poisoned seriously and almost fatally with arsenic about

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one year previous to the test. The one at four years is presumably a prostitute. One at seven years had Hutchinson's *teeth*. The other at seven years gave a history of an initial lesion and a short course of treatment eight years previously. The remainder of the patients gave no evidence or history of infection.

Up to an interval of four years, then, those mothers who gave negative Wassermann tests, gave either a history of infection or of treatment or both. After four years one gave a history of infection and treatment and another had Hutchinson's teeth. This leaves but six cases (four years, ten years, thirteen years, thirteen years and thirteen years) to whom no such suspicion is attached, and with the exception of the four-year case (presumably a prostitute) these mothers were examined at least ten years after the birth of their last syphilitic child.

It is easily conceivable that these mothers had had syphilis but that the infection had quieted to the extent of a negative Wassermann by the time they were examined. It would seem that a syphilitic infection really does have a tendency to die out, as does also its transmissibility to children, as will be shown later. Four of these mothers with negative reaction have borne children with negative reactions by the same father since their last child with positive Wassermann, which is further evidence that the infection is dying out. It is also significant that, though in all but two cases the syphilis in this group of mothers was presumably latent, 86 per cent. gave a positive Wassermann, while most figures given for latent syphilis are much lower than this. The whole proof of germinal transmission lies in the supposed fact that women who are free from syphilis can give birth to syphilitic children. This is no proof whatever because it can not be proved that these mothers have not been infected. Warthin has demonstrated at necropsy *Spirochaete pallida* in the viscera of patients who before death gave a negative Wassermann reaction.¹

It is recognized by abundant and good authority that a negative Wassermann does not mean the absence of syphilis. The Wassermann reaction is looked on merely as one of the symptoms of syphilis, but it is the most constant symptom, and in active syphilis it is negative only under fairly definite circumstances. On the other hand, to assert that a positive Wassermann invariably meant syphilis, would be unwise, for it is authoritatively asserted that it may be positive in certain cases of scarlet fever, leprosy, scleroderma, yaws, carcinoma and malaria. These diseases can usually be ruled out, however, and in their absence a positive Wassermann constitutes a valid proof of syphilis and indi-

1. Warthin, A. S.: Personal communication.

cates that the infection is actually present at the time of examination and is not due to syphilis in the past.

One of the mothers having a positive Wassermann refused treatment because there was nothing the matter with her and never had been. She returned a year later with tertiary lesions in her nose and throat. Rabbits have been successfully inoculated from the blood and milk of latent syphilitics whose only symptom was a positive Wassermann.² We also know that in certain cases of paresis and tabes the interval between the initial lesion and these affections may be thirty to forty³ years. Colles' law, that a syphilitic child even though it have lesions in the mouth never causes syphilis of the mother's breasts, has been abundantly proved. But the mother remains unaffected not because she is immune, but because she has the disease.

It is interesting to note that of the group of eighty-five mothers, seventy-four (87 per cent.) deny all knowledge of the infection, nor do they give any history other than of abortions which can be interpreted as symptoms of syphilis. Of those who give positive Wassermann reactions, sixty-seven out of the seventy-three give a negative history. This negative history can not be used as strong evidence against infection, for in women showing active lesions of syphilis more often than not, no chancre has been seen.⁴

SYPHILIS IN THE FATHERS OF SYPHILITIC CHILDREN

In most of the fathers of this group the infection was latent at the time of marriage, and a relatively small number give a history of active symptoms after marriage. Evidence is accumulating that spirochetes localize early in the testicle, even though they may not produce active lesions at this point. Nichols⁴ states that "experience has shown that the testicle rarely escapes." Warthin¹ states that in his necropsy material there were active lesions in the testis in all cases of latent syphilis. This would easily explain how an apparently healthy father can infect his wife. In such a case there would be a contact exposure just as surely as if a primary lesion existed.

SYPHILIS IN THE OFFSPRING OF SYPHILITIC PARENTS

As the result of syphilis numerous families remain sterile. The figures for sterility vary from 10 per cent. to 30 per cent., depending on the material studied. When there is an embryo there is a variety of fates to which it may come. Many marriages result only in abor-

2. Heiman: Jour. Am. Med. Assn., 1915, lxiv, 1463.

3. White: Jour. Am. Med. Assn., 1914, lxiii, 459.

4. Nichols: Jour. Am. Med. Assn., 1914, lxiii, 466.

tions (nearly 13 per cent. in Haskell's material⁵). Since the starting point in our material was a syphilitic child, we have no data bearing on this phase.

Among our syphilitic patients all the living children of 100 families have been examined, Wassermann tests made and the family history studied. In these 100 families there were 331 pregnancies. Of these 100 (30.2 per cent.) were abortions, 31 (9.3 per cent.) still births and 200 (60.4 per cent.) living births. Of the 200 living births 35 children died early and 4 died late, and 161 remained alive and were examined. Of these, 12 are now dead. Of the 35 who died early, 5 gave an undoubted history of syphilis and a number gave suspicious histories. Of the four who died late, one was an idiot. Of the 161 examined, 107 were clinically positive and had positive Wassermann tests. Five were clinically positive and had negative Wassermann reactions. Sixteen, who showed no evidence of syphilis, gave positive Wassermann reactions. Thirty-three, who gave no clinical proof of syphilis, gave a negative Wassermann reaction.

Of the five who were clinically positive but gave negative Wassermann reactions, one was a young infant who had snuffles and a large spleen. The mother and sister both gave a positive history and a positive Wassermann reaction. Shortly after beginning treatment the baby developed a syphilitic rash. The baby was removed from the hospital and a second Wassermann was not done. The second case was a nursing baby. The mother had active syphilis and was taking treatment. The baby had an active process in the nose. The third case was a 7-year-old girl who had a markedly sunken nose and who for that reason was the starting point for investigating that family. Both the mother and younger brother gave a positive Wassermann. The fourth case was a 4-year-old girl whose mother and younger sister were both positive and the patient had a general rash which was thought to be syphilitic. The fifth case was a 3-year-old boy with a positive history, and who had had some treatment. His mother and younger brother both had syphilis.

A negative Wassermann reaction is obtained in the presence of active syphilis only under certain definite conditions. As had been noted in cases not of this series, very young babies, even with undoubted active syphilis, not infrequently give a negative Wassermann. It has also been noted that even small amounts of mercury tend to cause a positive blood to react negatively.

H. Boas⁶ states that of fifty-seven babies of syphilitic mothers giving negative Wassermann reactions at birth, thirteen during a

5. Haskell: Jour. Am. Med. Assn., 1915, lxiv, 890.

6. Quoted by Haberman: Jour. Am. Med. Assn., 1915, lxiv, 1146.

three months' period of observation developed syphilitic manifestations and a positive Wassermann, and two others showed syphilitic changes at necropsy, having had no manifestations during life.

LATENT SYPHILIS

It is seen that 10 per cent. of the children examined had latent syphilis, i. e., a positive Wassermann and no clinical evidence of syphilis. One of these children gave a history of epiphysitis at 3 months. Other than this no early history was acknowledged by any of the mothers. The question naturally arises, Are these children actively infected with syphilis? When we inquire into the history of those showing late manifestations, we frequently find, so far as obtainable history is concerned, that there has been no previous warning that the disease existed. One of our patients developed, as her first known symptom, an interstitial keratitis at 20 years. We know that the spirochete can lie dormant much longer than this and then manifest itself. One patient of this latent group who had taken very irregular treatment for about a year and who had never had previous manifestations, recently developed an active lesion in the throat. Another developed an interstitial keratitis after about two months of anti-syphilitic treatment. A positive Wassermann reaction in these apparently healthy children has the same significance that it does in the parent, and it is our belief that the children in this group are actively infected.

The fact that there are thirty-three children, 10 per cent. of the total pregnancies, who show no evidence of syphilis, and at the same time give a negative Wassermann reaction, is rather hopeful. Yet the pleasure to be taken in this fact is not altogether unalloyed. In this small group there were two mental defectives and an idiot, and it is impossible to say that all of this group are free from syphilitic infection. In one instance, one such negative child returned about a year after his original examination with a tertiary type of lesion and a positive Wassermann. Though no classification of those in this group showing stigmata of degeneration was attempted, it can be truthfully stated that a goodly proportion did show degenerative influences, either physical or mental.

TOTAL SYPHILIS IN THE FAMILIES STUDIED

In summing up the total syphilitic infection in these families, we find that where marital relations are uninvolved, all of the fathers and probably all of the mothers have been infected. Presuming that the abortions, stillbirths, all of the early deaths and at least one of the late deaths were due directly or indirectly to syphilitic infection,

syphilis among the offspring amounts to 89 per cent. of the total pregnancies, and total syphilis in the family amounts to 93 per cent. of all its members.

DECREASING GRADES OF INFECTION IN THE OFFSPRING

In 1876 Kassowitz announced the general rule that the degree of transmissibility of syphilis gradually diminished in proportion to the duration of the disease. The first pregnancies are likely to be early abortions followed by late abortions and stillbirths, then by living children with decreasing grades of infection, and finally by normal children. Our series shows that any one family does not necessarily go through this list from the beginning, but may start from any one point and from there on continue with the decreasing infection. The start may be even as late as healthy children, as in one family now under observation.

In studying this series we find that this rule remains on the whole correct. In many cases it would seem as if there is a general tendency for the infection to die out both in the parent and in the child, or at least to localize in the mother in places where it is not readily transmitted to the fetus. This would explain the nonsyphilitic children of a mother with latent syphilis. In sixty-nine of our families in which the order of pregnancies was ascertained and all of the living children examined, forty-four families followed Kassowitz's rule and twenty-five varied more or less from it. If in four families the first child, being apparently nonsyphilitic, could be excluded on the ground that the mother was not yet infected, these families would otherwise have followed the rule. In no case was there a complete reversal of the rule, but in one family there was first a nonsyphilitic child, then a negative child with a positive Wassermann, followed by seven stillbirths and then a living birth in which the child was syphilitic. Nonsyphilitic children were interspersed between syphilitic children in seven instances in five families. For the most part the variation from the rule consisted of abortions following living syphilitic children, so that in a large measure in these twenty-five irregular families Kassowitz's rule was followed.

It has been thought by some, but not proved, that the more intense the disease in the parent the less severe it is in the surviving children. This does not appear to be the case. So far as we have been able to determine in this study, the starting point in Kassowitz's scheme is not determined so much by the severity of the infection in the parent as by the length of time elapsing between the infection and the first pregnancy. It has frequently been stated that the infection is much more probable and more severe in the children if the mother and not

the father is diseased. We believe the evidence shows that all mothers of syphilitic children have been infected, and it is quite reasonable that the infection in the child is more likely if the infection in the mother is active to the point of recognition than if it were not.

NONSYPHILITIC CHILDREN OF SYPHILITIC MOTHERS

In eight families of this group there are twelve apparently non-syphilitic children who follow syphilitic children and whose mothers still give positive Wassermann reactions. That the infection in the mother has become localized in such places that it is difficult of transmission to the offspring, would seem to be a reasonable explanation. Nor do these children necessarily prove immunity on the part of the child. They probably do not acquire it from the mother after birth for the same reason that they do not before birth, viz., its localization in unexposed parts.

EVIDENCE OF A NEUROTROPIC STRAIN OF SPIROCHETE

The idea that there are various strains of spirochete is becoming more and more established. Some seem to think the variations are a matter of the race of people infected and their racial reaction to the infection. This, however, does not seem to be true. Inland in China syphilis is common, but parasyphilis is quite rare; but in the Chinese who have brought syphilis from other countries or who have acquired it in coast ports, the incidence of parasyphilis is similar to that in this country.⁷ The greatest support of the idea of different strains of spirochete is based on its apparent predilection for the nervous system in certain groups with the same infection and the relative absence of this predilection in other groups with the same infection. In the families of this series this is shown very strikingly in a few instances.

FAMILY I. W.—Father has paresis. Mother recently had tertiary lesions in her nose and throat. First and third children have cerebrospinal syphilis. The second child recently had tertiary lesions in her throat.

FAMILY C. M.—Father died of paresis. Mother gives a positive Wassermann. First pregnancy resulted in a miscarriage, second a stillbirth, and of the third the child has cerebrospinal syphilis.

FAMILY H. W.—Father well. Mother has paresis. Four miscarriages. First living child died of convulsions at 9 days. Second and third children have cerebrospinal syphilis.

FAMILY W. B.—Father died of aneurysm. Mother well. First pregnancy resulted in a stillbirth. The child born of the second is 14 years old, gives a positive Wassermann reaction and is hysterical. The third pregnancy resulted in a miscarriage. The child of the fourth has cerebrospinal syphilis. Children of the fifth and sixth are mentally deficient, but give a negative Wassermann reaction.

7. Reed: Jour. Am. Med. Assn., 1915, lxiv, 1383.

In the remaining six families in which cerebrospinal syphilis appears in the child there are but eight living births. None of the others had so far developed this manifestation. One of the fathers committed suicide.

MISCELLANEOUS OBSERVATIONS

In three families we have what is apparently an infection of the mother by the first husband and a failure of the mother to infect the second husband in two instances, and in the third he was not infected until seventeen years after marriage. This observation was based on histories and Wassermann tests on the families as they exist at present. In each instance the mother continued to bear syphilitic children in the second marriage. In two instances the mother denied any knowledge of the disease.

One family deserves especial mention for the long period of infectivity of the mother. The father was infected before marriage. The mother denies all knowledge or symptoms of syphilis. The child of the first pregnancy is now 20 years old and very recently developed an interstitial keratitis, with no previous manifestation, and gives a positive Wassermann reaction. This child was followed by three miscarriages and six living births, two of which children died in early infancy. The remaining four, the youngest being 2 years old, all give positive Wassermanns, and two of these show manifest syphilis. The mother has taken no treatment and now gives a strongly positive Wassermann reaction.

Though there are several mothers in this group with signs commonly seen in hereditary syphilis, this series offers no proof one way or the other as to the transmissibility of syphilis to the third generation. Clark⁸ has reported a case of acute visceral hereditary syphilis in a 24-year-old woman. These late cases are not rare. I see no good reason why it is impossible for the 20-year-old girl mentioned above or Clark's 24-year-old patient to transmit syphilis to offspring. Such an event is not only possible, but in a very small number of cases probable.

SUMMARY

Germ transmission of hereditary syphilis has not been proved, and it does not seem likely that it ever occurs.

It is highly probable that all the mothers of syphilitic children have been infected with syphilis. Of eighty-five mothers of syphilitic children 86 per cent. gave positive Wassermann reactions. All of the remaining cases but six gave a history of infection or treatment, or both. Five of these six patients were examined at least ten years after

8. Clark: *Jour. Am. Med. Assn.*, 1914, lxii, 1167.

the birth of their last syphilitic children and the infection is probably dying out.

Eighty-seven per cent. of the mothers deny all knowledge of the infection. The mothers are for the most part infected during the latent stage of the father.

Of 331 pregnancies in 100 families, 30 per cent. were abortions, 9 per cent. stillbirths, 61 per cent. living births. Of the living births 24 per cent. had died. Of those living 80 per cent. had syphilis.

Of the total pregnancies 90 per cent. were presumably syphilitic and although 10 per cent. seem free from syphilis, there is no proof that they all are. The total syphilis in these families amounts to 93 per cent. of the entire family.

For the most part our families followed Kassowitz's rule; i. e., decreasing grades of infection in the children.

In case of syphilitic mothers bearing nonsyphilitic children, it is probable that the infection in the mother is localized in places where it is not readily transmitted.

The idea that there are different strains of spirochetes receives some support from these families.

Transmission to the third generation, though not proved, is distinctly an occasional probability.

SOME INTERESTING FACTS PLAINLY BROUGHT OUT BY
A CHART METHOD OF STUDYING AND MANAGING
CASES OF DIABETES MELLITUS IN CHILDREN*

DEWITT H. SHERMAN, M.D.

BUFFALO

Charts give one in the easiest and quickest way a fund of information concerning a case. In many febrile diseases valuable impressions are often gained if the whole course of the temperature is before one's eyes. This applies to diseases of long duration, such as diabetes mellitus, if it can be simply charted. This can be done, and the ones I show contain all the information necessary, and yet are not too cumbersome. They tell you what you have done, when you did it, and the results.

The upper half of my charts shows in unbroken lines the number of grams of the three food elements ingested, and their total caloric value. The lower half shows in broken lines the urine analyses, and hence the condition of your patient on the selected diet.

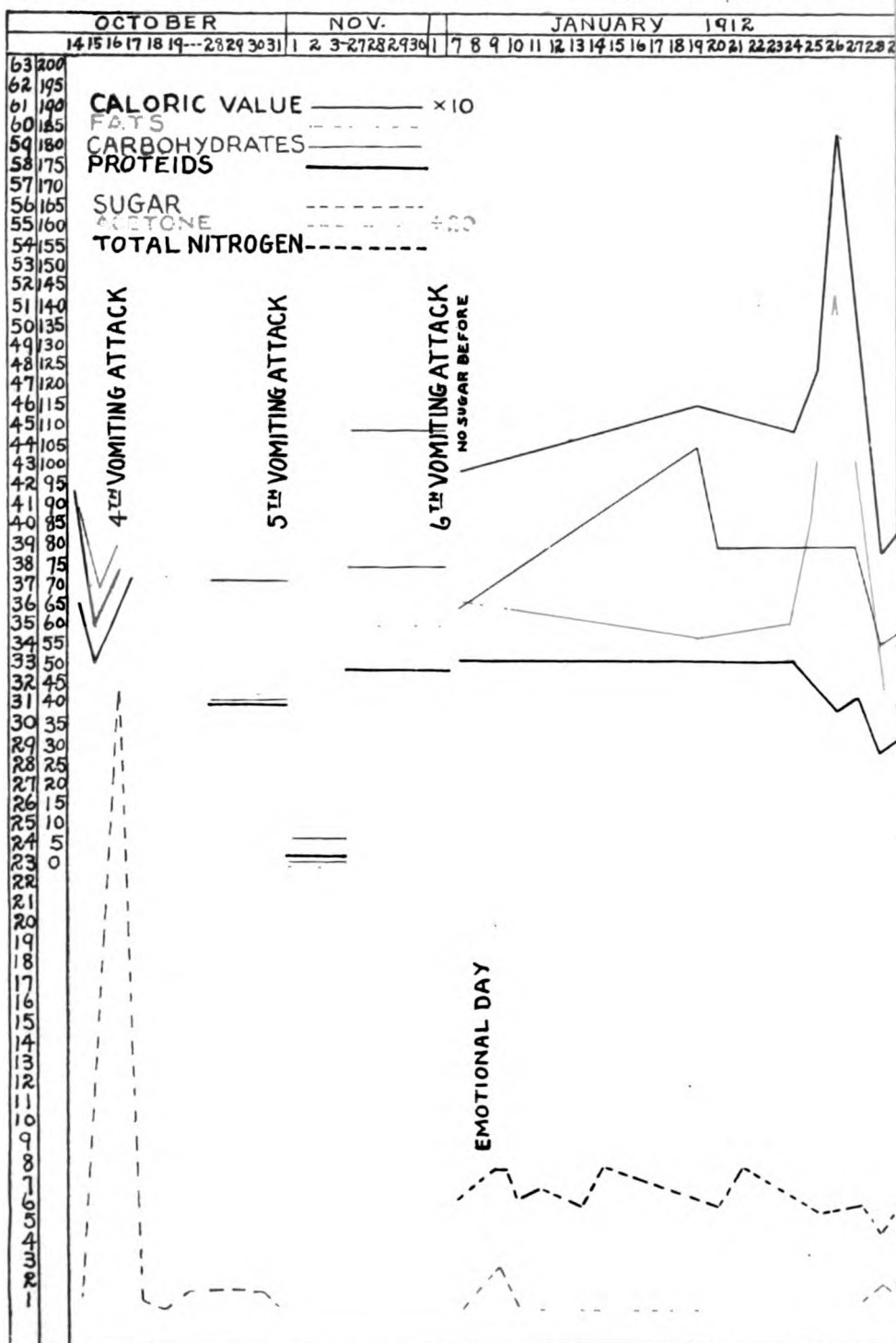
For further ease of reading, colored crayons are used. The continuous red line above shows the number of grams of carbohydrates ingested, and the lower broken red line shows the amount of sugar in the urine. The upper broken black line shows the proteins ingested, and the lower broken line the amount of urea.

The unbroken lines above of violet and blue show, respectively, the amount of fat ingested, and the caloric value of the diet. The broken lines below in brown, green and violet show the amount of urine, of ammonia-nitrogen, and of acetone eliminated. To save breadth of chart the figures on the side line must be multiplied by 100 for the amount of urine. Because the amount of ammonia-nitrogen and acetone are too small for charting purposes they must be multiplied by ten and twenty, respectively, and then charted. With these few points of explanation understood one can at a glance grasp the whole situation.

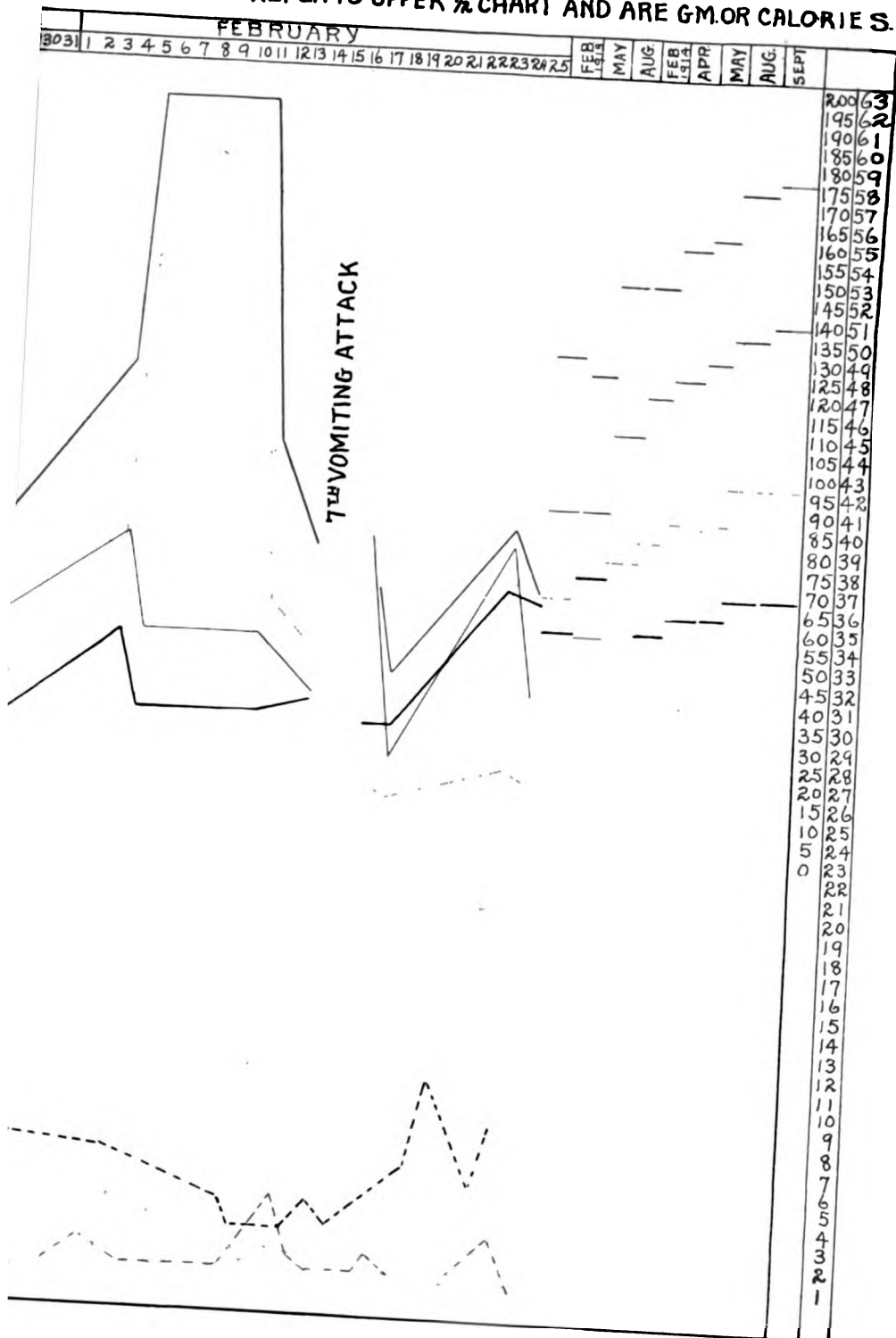
In the first chart shown skimmed milk was first given, because we were told the child of eight years could not easily tolerate fats. This allowed us very definitely to study her carbohydrate tolerance in the form of milk sugar. Because the amount of sugar fell on skimmed milk from 27 gm. in the first twenty-four-hour sample to 5.5 gm., we definitely learned that her milk sugar tolerance was poor. Not till all the milk was prohibited was she sugar-free. We learned, as shown,

* Read at the meeting of the American Pediatric Society, Lakewood, N. J., May, 1915.

CASE II 1911. OUTER COLUMNS OF FIGURES REFER TO LOWER 1/2 CHART AND ARE GM. OR



INNER COLUMNS REFER TO UPPER 1/2 CHART AND ARE GM. OR CALORIE S.



that she could be sugar free on meat, eggs, and butter, but as soon as a fodder food, such as onions, was given, she passed 4/10 as much sugar in the urine as she had ingested carbohydrates in the onions. While she tolerated meat and eggs well, when fish was added the amount of sugar which appeared was about 1/6 of the amount of fish ingested. This was peculiar.

The acetone was always present and gradually increased on all diets given. This alone showed, that in spite of the fact she was sugar-free, she was losing ground. As the acetone increased so did the ammonia-nitrogen, and this was another sign of unfavorable progress.

As regards Chart 2, the following points are of interest: With neurotic tendencies and a precocious intellect, this girl of 10 years was a victim of cyclic vomiting. We have charted four attacks of vomiting, and before three of these sugar appeared. Naturally it quickly disappeared on the starvation of persistent vomiting. It has consequently occurred to me that in cases of cyclic vomiting we might find sugar just before an attack more often than we suspect, due probably to the same faulty metabolism, which causes the vomiting. We tested the fat tolerance twice, as shown on the charts. The first time we gave 145 gm. and promptly sugar appeared. The second time we gave 165 gm. per day for six days. Soon sugar (2.50 gm.) appeared and decreased to 1.00 gm., when the carbohydrates were reduced much below a well known carbohydrate tolerance. After the high fats were lowered below a well known tolerance, the sugar not only persisted but rose to 5 gm., and she had a vomiting attack. This late rise in sugar and the vomiting were then, without doubt, due to the damage done by the fats. I could then conclude, (1) that an excess of fat may in itself cause sugar to appear, and (2) that high fat may be a cause of cyclic vomiting.

This second statement has been proved in her case, because, since her fats have been kept at 100 gm. or less per day, she has not vomited. As regards the acetone, the fats caused it to increase.

I mentioned above that the child was a neurotic. One day, as shown, sugar appeared while we were testing the carbohydrate tolerance. As no clear cause was seen we kept on increasing the carbohydrates, and in spite of this increase the sugar disappeared. On very thorough investigation we learned that the sugar was undoubtedly due to the worry of a guilty conscience, because she had been for weeks doing something she knew was not right. This shows that an unbalanced nervous system can produce sugar.

The chart in her case shows no idiosyncrasy to any of the different starches, proteins, or fats. They were all equally tolerated. Her tolerance to milk sugar in milk and levulose in fruits was only fair, and no different from any other starch.

The third chart I do not show. At varying intervals I give the usual starvation or water day. This boy of four years on one of these days vomited, with nervous manifestations, going into more or less of a stupor. This I experienced once in another child, except that the second child was delirious. No cause have I found for such an upset in either case.

SUMMARY

Charts aid materially in the study of a case of diabetes.

In one of my cases sugar was caused (1) by high fats, and (2) by mental anxiety.

In another, fish caused sugar, while all the other proteins were fairly well tolerated.

In one case high fats caused cyclic vomiting.

Sugar may appear before cyclic vomiting attacks more often than we suspect.

THE ETIOLOGY OF PACHYMEMINGITIS HEMORRHAGICA INTERNA IN INFANTS*

A. B. SCHWARTZ, M.D.

CHICAGO

Since the first accurate description of pachymeningitis hemorrhagica interna by Virchow¹ in 1856, observers have differed in their views regarding the exact nature of this condition. Virchow believed that the membrane formation on the inner surface of the dura precedes the hemorrhage. Huguenin² maintained that the hemorrhage is primary, the organization of the clot causing the membrane formation. The work of Melnikow-Raswedenkow³ and others supported Virchow's view, which has gradually become the prevailing one.

It was thought that most of the cases seen in the adult⁴ resulted from sclerotic changes incident to chronic diseases of the brain, heart, kidneys and lungs. Similarly, regarding cases occurring in the infant, the prevailing opinion seemed to be that pachymeningitis is secondary to other diseases, the cerebral changes being usually discovered at necropsy in infants dying from various infectious diseases, or in chronic cachectic conditions.⁵

Kremiansky⁶ performed experiments on dogs, showing the importance of alcoholism as an etiologic factor in the production of this disease. Needless to say, cases occurring in infancy cannot be explained by this hypothesis.

It has been maintained by many observers that cerebral hemorrhage occurring at birth is an important factor in these cases. Recent workers though emphasizing other factors in adults, still attribute to

* Submitted for publication Oct. 16, 1915.

* From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital.

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4. Ciarla, E.: *Beitrag zum pathologisch anatomischen u. klinischen Studium der Pachymeningitis cerebialis hemorrhagica*, Arch. f. Psychiat., 1913, lii, 439.

5. Holt, L. Emmett: *Diseases of Infancy and Childhood*, New York, 1913, p. 698. Steffen, A.: *Handbuch d. Kinderkrankheiten*, Tübingen, 1880, v, 380.

6. Kremiansky, J.: *Ueber die Pachymeningitis interna hemorrhagica bei Menschen und Hunden*, Virchow's Arch. f. path. Anat., 1868, xlii, 129 and 321.

such hemorrhage great importance in the production of this disease in infants.⁷

Boeckmann⁸ made a study of numerous cases coming to necropsy following various cranial operations. Most of these had had considerable hemorrhage following the operation. In no case could Boeckmann demonstrate any pachymeningitis; its absence, he thinks, disproving the importance of trauma as a cause for pachymeningitis.

Marie⁹ and his co-workers were unable to produce pachymeningitis hemorrhagica in dogs and rabbits by the subdural injection of blood.

In a series of 5,998 necropsies on children, Kowitz¹⁰ found intracranial hemorrhage present in 16.9 per cent., pachymeningitis in only 3.9 per cent. Among other causes given for this disease are syphilis,¹¹ scorbutus,¹² hemorrhagic diseases,¹³ and pertussis.⁷

Some observers¹⁴ have laid more or less stress on digestive disturbances in infancy as of possible etiologic significance, while others¹⁵ have noted that cases are occasionally brought to a hospital on account of alimentary symptoms, which often obscure the true nature of the disease.

The possibility of pachymeningitis being the result of a hemogenous infection is suggested by the case reported by Schottmüller¹⁶ of a woman 28 years old who died following a puerperal septicemia of streptococcus origin. The fluid obtained by lumbar puncture during life showed an excess of globulin, the cell count was 181, cultures

7. Hada, B.: Ueber die gehirnkomplicationem des Keuchhustens mit besonderer Berücksichtigung der Pachymeningitis productiva interna, *Virchow's Arch. f. path. Anat.*, 1913, ccxiv, 206. Wohlwill, F.: Ueber Pachymeningitis hemorrhagica interna, *Virchow's Arch. f. path. Anat.*, 1913, ccxiv, 388.

8. Boeckmann, M.: Ein Beitrag zur Ätiologie der Pachymeningitis interna hemorrhagica, *Virchow's Arch. f. path. Anat.*, 1913, ccxiv, 380.

9. Marie, P.: Roussy, G., and Laroche, G.: Sur la reproduction expérimentale des pachyméningites hémorragiques, *Compt. rend. Soc. de biol.*, 1913, lxxiv, 1303.

10. Kowitz, H. L.: Intrakranielle Blutungen und Pachymeningitis hemorrhagica chronica interna bei Neugeborenen und Säuglingen, *Virchow's Arch. f. path. Anat.*, 1914, ccxv, 233.

11. Heubner, O.: Pachymeningitis hemorrhagica bei hereditärer Syphilis, *Virchows Arch. f. path. Anat.*, 1881, lxxxiv, 267.

12. Sutherland, G. A.: On Hematoma of the Dura Mater Associated with Scurvy in Children, *Brain*, 1894, xvii, 27.

13. Oppenheim, H.: *Lehrbuch d. Nerven krankheiten*, Berlin, 1908, p. 849.

14. Misch, P.: Zwei Fälle von Pachymeningitis hemorrhagica interna, *Jahrb. f. Kinderh.*, 1905, lxii, 229. Poulet, Anna: Ein fall von Pachymeningitis nicht traumatischen natur im Kindesalter, *Inaug. Dissert.*, Zurich, 1902.

15. Göppert, F.: Drei Fälle von Pachymeningitis hemorrhagica mit Hydrocephalus externus, *Jahrb. f. Kinderh.*, 1905, lxi, 51. Meigs, Grace: *Jour. Am. Med. Assn.*, 1913, lxi, 2186.

16. Schottmüller, H.: *Pachymeningitis interna infectiosa acuta und Meningismus*, München. med. Wchnschr., 1910, lviii, 1984.

were sterile. Postmortem examination revealed a pachymeningitis. Göppert thinks that Krücke's¹⁷ case of pachymeningitis demonstrated in a child dying from pharyngeal and laryngeal diphtheria illustrates a similar possibility. Krücke's case lacks the clinical history prior to death, nor was Krücke able to demonstrate diphtheria bacilli in the lesions, attributing his failure to the fact that the necropsy was not done until sixty hours after death.

Until recently there were few cases of this disease reported in infancy. Finkelstein¹⁸ and Göppert¹⁵ not only described a definite clinical picture occurring in pachymeningitis, but were the first to call attention to its more frequent occurrence in infancy than had been previously recognized.

Rosenberg,¹⁹ reporting thirty-eight cases, divides the disease into three types:

1. A latent form, in which class of cases there may be seen slight restlessness, no nervous symptoms, enlargement of the head, with separation of the sutures and fontanels.

2. A form with acute nervous symptoms. In these cases, the onset occurs with vomiting. Restlessness, the "hydrocephalic cry" and convulsions follow. The reflexes are exaggerated, and there may be spasm of the extremities.

3. A fulminating form in which the patient is in coma, has frequent convulsions and rigidity of the neck. These are the cases which are usually diagnosed as meningitis. There is usually not much fever.

The enlarged head and separation of sutures, suggesting hydrocephalus, is present in all types.

Retinal hemorrhage is of great diagnostic importance, occurring in one-third of Rosenberg's cases. Optic atrophy is occasionally found; choked disk may be present.

Lumbar puncture usually gives a clear fluid under increased pressure. Occasionally, one may get bloody spinal fluid, which always indicates a tear in the arachnoid.²⁰ Hemorrhage due to accidental puncture of a vein during lumbar puncture must be excluded. Hemorrhagic fluid obtained on fontanel puncture is of great diagnostic value. This fluid may be truly hemorrhagic, or exhibit a brownish or yellowish coloration due to the presence of old blood. Rosenberg

17. Krücke, L.: Ein fall von eitrig entzündeter Pachymeningitis hemorrhagica bei Difterie, Inaug. Dissert., Kiel, 1902.

18. Finkelstein, H.: Ueber Pachymeningitis hemorrhagica im Kindesalter, *Jahrb. f. Kinderh.*, 1911, lxxiv, 451; *Berl. klin. Wchnschr.*, 1904, xli, 403.

19. Rosenberg, O.: Ueber Pachymeningitis hemorrhagica im Kindesalter, *Berl. klin. Wchnschr.*, 1911, I, 2272.

20. Quincke, H.: Ueber Lumbalpunktion, *Deutsche klin.*, Berlin, 1906, vi, Part 1, p. 351.

found that 80 per cent. of his cases showed the presence of rhinitis, from which the diphtheria bacillus was isolated. He attributes to this rhinitis considerable etiologic importance. The ethmoidal veins which supply the nasal mucous membrane empty into the ophthalmic veins, which empty into the cavernous sinus. Rosenberg thinks there is a possibility of erosions on the nasal mucous membrane causing a sinus thrombosis, which may produce the pachymeningitis. He attempts to explain the case reported by Heubner, which the latter had attributed to congenital syphilis, on similar grounds, believing the coincident rhinitis to be the possible explanation for the presence of pachymeningitis.

Only recently has more attention been called to the possible infectious nature of pachymeningitis in infancy.

Göppert, in 1905, reporting three cases, expressed the opinion that a primary serous subdural exudation occurred in pachymeningitis. He found no similar suggestion in the previous literature on the subject.

Hahn²¹ reported a case in which he was able to demonstrate an actual serofibrinous exudate.

In a study of the relationship of pertussis to pachymeningitis, Hada⁷ concludes that toxins or bacteria first produce an infection which is subsequently followed by hemorrhages.

The actual occurrence of symptoms of serous meningitis preceding the development of hydrocephalus in a case, which after death showed pachymeningitis, suggests to Freund²² the possibility of pachymeningitis being of an infectious nature.

Though Rosenberg demonstrated a streptococcus in the bloody fluid obtained from two patients with pachymeningitis, one of whom recovered, and one of whom died with a streptococcus meningitis, he lays no stress on the isolation of the streptococcus in these cases.

Excepting this finding of Rosenberg, in all recent reported cases²³ of pachymeningitis which have included bacterial examinations, no organisms have been demonstrated in the spinal fluid.

Finkelstein¹⁸ concludes that bacteriologic study of this disease has not shown it to be of an infectious nature.

21. Hahn, H.: *Klinischer Beitrag zur lehre von der Pachymeningitis hemorhagica interna im frühen Kindesalter*, Deutsch. med. Wchnschr., 1911, xxxvii, 1518.

22. Freund, W.: *Zur Therapie des Hydrocephalus zugleich ein Beitrag zur Kenntnis der Pachymeningitis hemorhagica im Sauglingsalter*, Monatschr. f. Kinderh., 1909, vii, 613.

23. Gordon, A.: *Internal Pachymeningitis in Young Children*, Jour. Nerv. and Ment. Dis., 1914, xli, 382. Hartje, E.: *Zur Casuistik der Meningitis basilaris posterior*, Arch. f. Kinderh., 1912, lvii, 333. Schindler, R.: *Ein Fall von Meningocele spuria traumatica kombiniert mit Pachymeningitis hemorhagica interna*, Jahrb. f. Kinderh., 1912, lxxvi, 160.

The diagnosis of the case to be reported was that of pachymeningitis. It is based on the clinical picture entirely.

In this picture there stand out prominently the repeated bloody character of the spinal fluid, the severe retinal hemorrhages, and the fact that the subdural fontanel puncture yielded an amber colored fluid. All of these features have been accepted by Rosenberg and others as indicating the presence of pachymeningitis. Naturally there exists the possibility that we are dealing with a particular case of leptomeningitis, or encephalitis with pronounced hemorrhagic lesions. The lack of a necropsy does not permit the absolute exclusion of such possibilities. If so, then a number of cases reported in the literature as pachymeningitis on purely clinical evidence are subject to the same objections.

Even accepting such possibilities, these cases become important, inasmuch as they may be gradations between the usual form of leptomeningitis and pachymeningitis.

The case herewith reported is one in which the meningococcus was demonstrated in the spinal fluid on several separate examinations.

REPORT OF CASE

History.—Jennie P., Polish girl, born January, 1915, was admitted to The Children's Memorial Hospital, May 10, 1915, on account of convulsions and diarrhea.

Family History.—Parents living and well. No other children. No miscarriages. No known history of tuberculosis in family.

Past History.—Protracted labor, no forceps used. Birth weight 9¼ pounds. No respiratory trouble following delivery. Breast fed one week, following which the infant was fed on various milk mixtures. Feeding intervals irregular. At two weeks she had furunculosis. At four months the patient had three convulsions, cause unknown. Was treated in Out-Patient Department three weeks prior to admission for fracture of left humerus.

Present Illness.—Began May 3, 1915, with convulsions, which recurred frequently for twenty-four hours. Then followed two days, during which time, no convulsions occurred.

May 6, 1915, convulsions recurred, continuing since. Had had a diarrhea; stools described as foul, green, watery. Had had a slight cough; no vomiting.

Physical examination showed an under-nourished baby with no abnormal findings.

During a four-days' stay in the hospital, the temperature was normal, the stools appeared normal, the infant had no convulsions, and gained 9 ounces on a mixture of $\frac{2}{3}$ whole milk and $\frac{1}{3}$ water, with 3 per cent. additional dextrin-maltose.

The case was considered one of convulsions due to improper feeding and the patient was discharged May 14, 1915. May 17, 1915, she was readmitted. The mother stated that the child had a convulsion shortly after returning home and cried much that day and the next. On the second day home the patient vomited and had vomited persistently since. For the previous two days had appeared too weak to cry. Bowel movements normal.

Physical Examination.—Semicomatose. Extremely pale. Does not resist examination. Respirations regular but shallow. Emaciated. Very poor tissue turgor. Corneae dull, eyes fixed.

Head: All sutures of skull widely separated. The anterior fontanel was tense and bulged considerably. Slight craniotabes present. Head appeared large in comparison to body.

Eyes: Pupils equal, left did not react to light. Right pupil reacted sluggishly.

Ears, Nose, Mouth and Throat: Nothing abnormal noted.

Thorax: Rachitic rosary present.

Heart: No abnormality noted.

Lungs: Few mucous râles scattered over chest. No dulness. No abnormal breath sounds.

Abdomen: Level and tympanitic. Liver edge felt 4 cm. below costal margin. Spleen not felt.

Extremities: Slight rigidity.

Laboratory Reports.—White cell count, 20,600.

Hemoglobin (Tallquist), 65 per cent.

Differential Count:

Polynuclears, 76 per cent.; small mononuclears, 14 per cent.; large mononuclears, 6 per cent.; basophils, 4 per cent.

Wassermann: Negative.

Vaginal Smear: No gonococci found.

Urinalysis: Nothing abnormal found.

Throat and Nasal Culture: Negative for diphtheria bacilli.

Von Pirquet reaction negative.

Roentgenogram of head and chest negative.

Lumbar Puncture: Sixty c.c. bloody fluid under increased pressure. Hang-drop shows field full of red blood cells, no organisms seen. Cultures made show growth, within twelve hours, of a large bacillus (contamination).

May 18, 1915. Lumbar puncture: 3 c.c. bloody fluid, no examination made. Left lid drooping. Left foot and hand show occasional twitching.

May 19, 1915. Fronto-occipital circumference, 40.5 cm.

May 20, 1915. Ophthalmoscopic examination (Dr. Alfred Hall): Chorio-retinitis with marked hemorrhage throughout both retinæ.

May 22, 1915. Lumbar puncture: 5 c.c. bloody fluid under increased pressure. Cultures made in bouillon. After thirty-six hours' growth, diplococcus isolated.

May 25, 1915. General condition somewhat improved. Color better. Responds more to stimuli. Has fairly normal cry during examination. Opens eyes, but apparently does not see. Fontanel tense. Pupils unchanged. Suggestive Kernig's sign on left side. Brudzinsky sign present. Slight spasticity of extremities.

May 27, 1915. Lumbar Puncture: 20 c.c. bloody fluid under increased pressure. Cultures made in human blood agar and plated. After twenty-four hours diplococcus isolated.

May 29, 1915. Lumbar Puncture: 40 c.c. amber colored fluid, under increased pressure. Unstained smears show crenated and degenerated red cells. No organisms; 10 c.c. antimenigitis serum given. Cultures made in bouillon and human blood agar; diplococcus isolated.

May 30, 1915. Patient lies very quietly, but cries when disturbed. Piercing shriek when extremities are manipulated to elicit reflexes. Knee jerks not obtained. No Kernig's sign. Marked spasticity of extremities. Fronto-occipital circumference 42.5 cm. General appearance of hydrocephalus.

May 31, 1915. Lumbar Puncture: Sixty c.c. amber-colored fluid under increased pressure. Cultures made in litmus milk and on plain agar. No growth obtained.

June 2, 1915. Lumbar Puncture: Forty c.c. amber-colored fluid under increased pressure. Smears show many white and red cells and an occasional diplococcus. Cultures made on human blood agar; diplococcus isolated.

June 3, 1915. Ophthalmoscopic Examination (Dr. Alfred Hall): Extreme atrophy of both optic nerves. Hemorrhages of retina clearing up.

June 4, 1915. Lumbar Puncture: Forty c.c. clear yellow fluid under increased pressure. Smears show increased number of leukocytes, polynuclears predominating. No organisms. Cultures on human blood agar; no growth.

June 8, 1915. Lumbar Puncture: Forty c.c. bloody fluid under increased pressure. Cultures in bouillon; diplococcus isolated.

June 11, 1915. Lumbar Puncture: Thirty c.c. clear fluid under increased pressure. Cultures in bouillon; no growth.

June 26, 1915. Lumbar Puncture: Sixty c.c. fluid; first 30 c.c. clear, last 30 c.c. a pale yellow; pressure greatly increased. Cultures in bouillon; no growth. Furunculosis of scalp; furuncles incised; cultures made. Staphylococcus present.

July 13, 1915. Facial expression not as drawn, though there is still marked pallor and universal loss of tissue turgor. Sutures and fontanel are beginning to approximate themselves. Fronto-occipital circumference 41.5 cm.

July 27, 1915. Fontanel bulging somewhat. Lumbar puncture and fontanel puncture done. The fluid obtained at both points was under increased pressure. That from the fontanel (subdural) was amber colored, and on standing showed a deposit of blood. Cultures made in bouillon; no growth. The fluid obtained by lumbar puncture was perfectly clear. Cell count 50. Noguchi: Faint turbidity. Permanganate reduction index, 3.4. Excepting for a short interval when patient had furunculosis, the temperature remained normal throughout illness. Weight practically stationary. Aug. 14, 1915, patient began losing weight, failed steadily, and died August 23. No necropsy granted.

Bacteriology.—The organism isolated from this case of pachymeningitis was demonstrated in cultures of the cerebrospinal fluid obtained from five different lumbar punctures. The organism grew well on human blood agar and in bouillon. Subcultured, it grew on most of the ordinary laboratory culture mediums. On agar slants the growth appeared as slightly larger than pin-head, round, glistening, grayish-white, discrete, elevated colonies, which as growth continued formed a confluent streak with slightly irregular edges.

By Gram staining it appeared as a large gram-negative coccus, occurring in diplo, tetrad or group arrangement, which characteristics it retained in further subcultures.

Several observers²⁴ have reported the finding of other gram-negative diplococci than the meningococcus in the cerebrospinal fluid. Furthermore, the importance recently ascribed to the parameningococcus²⁴ as a causative agent in resistant cases of epidemic meningitis, made it necessary to determine by differential tests the exact nature of the organism isolated.

It has been shown by von Lingelsheim²⁵ that the meningococcus can be differentiated from other gram-negative diplococci by its reactions to various sugars. According to his work, the meningococcus changes dextrose and maltose, but not levulose, saccharose, galactose and lactose.

The medium used for the differentiation was prepared in the usual manner.²⁶

24. Kutscher: *Kolle-Wassermann Handbuch d. path. Mikro-organismen*, Jena, 1912, p. 589. Dopter, M.: *Diagnostic bactériologique des méningites cérébrospinales à méningocoques et à parameningocoques*; Societie med. d. Hôpitaux d. Paris, Series 3, 1914, xxxvii, 1217.

25. v. Lingelsheim, W.: *Klin. Jahrb.*, 1906, xv, 373.

26. Kolle-Hetsch: *Die Experimentelle Bakteriologie und du Infektionskrankheiten*, Berlin, 1911, p. 378.

The growth on this medium was slow in appearing, no culture showing growth before forty-eight hours, while some showed no growth before sixty hours. The colonies on the dextrose and maltose ascites agar soon turned pink, while those in the other sugars remained colorless or slightly blue colonies.

Albrecht and Gohn²⁷ were the first to note the occurrence of specific agglutinins in the blood serum of animals receiving repeated injections of meningococci.

Specific agglutinins in the serum of patients ill or convalescent from epidemic meningitis were first noted by Bettencourt and Franca.²⁸

Following the work of Dopter and others on the parameningococcus, agglutination through specific serum reactions is now considered the most trustworthy guide in the identification of the meningococcus.²⁹

While normal serums may agglutinate the meningococcus in dilutions of 1 to 20, serums containing specific agglutinins will agglutinate the meningococcus in greater dilutions.²⁸

The serums used in the present instance were as follows:

1. Jennie: Patient's own serum.
2. Stephanie: Serum of a convalescent epidemic meningitis patient who had responded to treatment with Flexner's serum.
3. Antimeningitis serum: New York State Board of Health.
4. Normal serum (author's blood).

A suspension of the organism having been made in 0.9 per cent. salt solution, various dilutions of the serum were then made to which were added the same amount of suspension. The tubes were placed in the incubator at 37 C. for two hours, then transferred to the ice chest for twenty-four hours.

The accompanying table gives the results of the agglutination determinations:

RESULTS OF AGGLUTINATION DETERMINATIONS

	1 to 40	1 to 60	1 to 80	1 to 100	1 to 120	1 to 160	1 to 320	1 to 640
Jennie's serum	+	+	—	—	±	—	—	—
Stephanie's serum	++	++	+	—	—	—	—	—
Antimeningitis serum	+	+	±	—	—	—	—	—
Normal serum	—	—	—	—	—	—	—	—

27. Albrecht, H., and Ghon, A.: Ueber die Aetiologie und path. Anatomie der Meningitis cerebrospinalis epidemica, Wien. klin. Wchnschr., 1901, xiv, 984.

28. Bettencourt, A., and Franca, C.: Ueber die Meningitis cerebrospinalis epidemica und ihren Erreger, Ztschr. f. Hyg. u. Infectiouskr., 1904, xlv, 463.

29. Flexner, Kraus and Levaditi: Handb. d. Technik, u. Methodik d. Immunitätsforsch., Jena, 1914. Quoted by Wollstein, M.: Jour. Exper. Med., 1914, xx, 201.

DISCUSSION

It appears probable that pachymeningitis hemorrhagica as it occurs in infancy is an infectious disease, which may be caused by the meningococcus or other organisms. That this possibility should have passed unnoted by students of pachymeningitis seems all the more remarkable when it is recalled that Weichselbaum³⁰ in his early work with the meningococcus was able to produce pachymeningitis and leptomeningitis and acute encephalitis by the injection of this organism.

His experiments were done on dogs, the injection of the meningococcus being made subdurally after trephining the skull. The dogs appeared well for several hours. After five or six hours they appeared sick. One dog died the same evening. The second, acutely ill, was killed on the third day. The third dog died on the twelfth day. The first two dogs showed fluid blood between the dura and the cerebrum, a hemorrhagic area of softening in the cerebrum, with much injection of the meninges. The third dog showed a thick reddish exudate between the dura and the brain, while in the brain substance there was an abscess the size of a hazelnut, and numerous hemorrhages.

It seems probable that pachymeningitis and leptomeningitis are but different manifestations of a single process, the meningococcus being the offending organism in both diseases.

In the light of Rosenow's³¹ work with the streptococcus, it seems possible that the meningococcus, in like manner, at one time may produce leptomeningitis, at another pachymeningitis. That transition forms of meningitis do occur, suggesting such a possibility, is evident from the studies of various epidemics of the disease. While the predominating feature of the usual case is an acute fibrinopurulent exudate involving the pia-arachnoid of the brain and cord, the dura is usually vascular,³² and hemorrhages in the brain and other organs are common. The extent of these hemorrhages varies considerably in various epidemics. Thus Bettencourt and Franca²⁸ in their studies on epidemic meningitis comment on the frequency of hemorrhages in their series, the histologic picture of the brain being often that of meningo-encephalitis hemorrhagica. Subarachnoidal hemorrhages are also noted by these observers.

As there are various forms of meningitis, produced by various organisms, it is quite probable that similar divisions occur among the

30. Weichselbaum, A.: Ueber die Aetiologie des akuten Meningitis cerebrospinalis, *Fortschr. d. Med.*, 1887, v, 620.

31. Rosenow, E. C.: *Jour. Infec. Dis.*, 1915, xvi, 240; *ibid.*, xvi, 367; *ibid.*, xvii, 219.

32. Westenhoeffer, M.: *Pathologisch-anatomischen Ergebnisse der Oberschlesischen Genick-starre epidemie von 1905*, *Klinisches Jahrb.*, 1906, xv, 657.

cases of pachymeningitis. Indeed, the cases reported by Rosenberg of pachymeningitis in which streptococci were isolated, and the case reported by Dupérié³³ in which tuberculous meningitis and pachymeningitis were present in the same case, confirm this idea. That organisms have not been isolated in these cases heretofore is probably due as much to the lack of search, as to the difficulty often encountered in their isolation.

33. Dupérié, R., and Dubourg, E.: Pachyméningite hémorragique. Hémorragie méningée et tuberculose encéphalo-méningée chez un enfant de deux ans, *Gaz. hebd. d. sc. méd. de Bordeaux*, 1913, xxxiv, 157.

PARAPNEUMONIC EMPYEMA *

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The term "*pleuresie parapneumonique*" was first proposed by Lemoine¹ in 1893, to describe the occurrence of fluid in the pleural cavity coincident with pneumonia. He pointed out the fact that the occurrence of fluid in the chest during the early part of an attack of pneumonia is more frequent than is generally supposed, occurring in possibly five to six per cent. (Grisale, 12.6 per cent.; Deustl, 16 per cent.; Fisser, 15 per cent.; Magnus Hus, and Jugenser, 4 or 5 per cent.). He further states that the fluid of parapneumonic pleurisy is always serous, while that of metapneumonic pleurisy, that following the crisis, is always purulent.

Le Damnay² in a thesis on pleurisies, in 1897, also calls attention to the occurrence of fluid in the thoracic cavity coincident with pneumonia, and gives histories of four such cases. Since these researches a large number of cases of parapneumonic pleurisy has been reported.

For his thesis in 1901 Siems³ collected twenty-six cases. All patients were adults. The amounts of fluid obtained varied from a few drops to 700 c.c. In two cases no puncture was made. From his data Table 1 is made with regard to the character of the fluid and the bacteriologic findings.

TABLE 1.—CHARACTER OF FLUID AND BACTERIOLOGIC FINDINGS

Type of Fluid	Micro-Organisms Present (Smears, Cultures, or Animal Inoculation)
Serous	8
Serofibrinous	11
Blood stained	1
Seropurulent	2
Purulent	2

In four of these cases the fluid obtained from the pleural cavity was purulent or seropurulent. They were as follows:

1. A patient 39 years of age with pneumonia. Puncture gave "5 c.c. of a liquid seropurulent, cloudy, very rich in pus cells." No micro-organisms in

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1. Lemoine: *Semaine méd.*, 1893, p. 12.

2. LeDamenay: *Recherches sur les pleuresies sero-fibrineuse primitives et secondaires*, Thèse, Paris, 1897.

3. Siems: *Les Pleuresies Contemporaines de la pneumonie*, Thèse, Paris, 1901.

smears or cultures. Inoculation into a mouse gave no result. The patient recovered, the fluid being absorbed.

2. Two days before death puncture gave 100 grams of "seropurulent fluid" containing many pneumococci. Inoculation of mice caused death, the pneumococci being recovered from their blood. At necropsy the patient showed gray hepatization of the right lung and a fibrinopurulent pleurisy.

3. A laborer four hours after a blow on the side was brought into the hospital with hemoptysis. Pneumonia started four days later and puncture gave 10 c.c. of sterile "pus." On the sixth day 10 c.c. of "purulent fluid," also sterile, was obtained. There was spontaneous absorption and uneventful recovery.

4. Patient aged 45 years. Puncture gave a few drops of "yellow fluid" from which a pure culture of pneumococci was obtained. Inoculation of mouse caused death in twenty-four hours. The patient died on the seventh day of his pneumonia. At autopsy "purulent fluid" was found encapsulated by fresh adhesions between the lung and mediastinum. Virulent pneumococci were found in this fluid also.

Widal and Gougerot,⁴ in 1906, describe two cases, comparing the fluid to that found in the cerebrospinal canal after certain syphilitic affections. They call especial attention to the presence in the fluid of large numbers of polymorphonuclear leukocytes which retain their morphologic and functional integrity, and the complete absence of any micro-organisms, as shown by smears, cultures and animal inoculation. They say also that these fluids resemble closely those resulting from the injection of sterile bouillon into the peritoneal cavity of guinea-pigs.

Their patients were 24 and 34 years of age, both having typical lobar pneumonia.

1. On the fourth day of the disease 5 c.c. of fluid was obtained by puncture. Two days later none could be obtained.

2. On the fourteenth day while the disease was still actively present 100 c.c. of fluid was obtained. Four days later only a few drops of "blood-stained fluid" could be removed. The fluids of both cases were sterile but opaque, containing many polynuclear cells.

Pende,⁵ in 1909, describes three cases, ages 13, 14 and 15 years, in which "purulent" fluid was obtained by puncture. These contained no organisms but many polymorphonuclear cells. They were absorbed spontaneously, one in three and the other two in four days.

Neuman,⁶ in 1912, reviews the literature and reports two cases which are later included in those reported by Gerhardt.⁷ He lays special stress on the fact that parapneumonic fluids are usually sterile.

4. Widal and Gougerot: Bull. et mém. Soc. d. hôp. de Paris, 1906, vii.

5. Pende: Policlinico, Rome, 1909; ref. Zentralbl. f. inn. Med., 1910, p. 513.

6. Neuman, K.: Parapneumonic Empyema, Inaugural Dissertation, Wurzburg, 1912.

7. Gerhardt: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, xxvi.

Dumont,⁸ in 1912, observed three cases.

1. A patient 26 years old had active signs of pneumonia. Punctures on the first and third days gave only blood. On the fourth day by puncture 20 c.c. of opaque "pus" was removed, which on centrifugalization gave a sediment and an opalescent supernatant fluid. The cells were 70 percent polymorphonuclear leukocytes. No organism could be found by cultures and inoculations gave no results.

2. A patient 52 years old. On the fifth day of pneumonia "some pus" was removed by puncture. On the eighth day "more pus" was removed. On the fourteenth day the Roentgen ray showed a shadow and on puncture "sero-fibrinous fluid" was obtained. On the thirty-second day there was evacuated completely 40 c.c. The fluid contained no micro-organisms.

3. A patient 24 years old. Puncture on the tenth day gave 20 c.c. of "purulent fluid," 70 per cent. polymorphonuclear cells. No micro-organisms by smears, cultures or inoculation. No fluid was found the following day.

Gerhardt,⁷ in 1913, reports five cases.

1. A patient 46 years old. Puncture on the second day of pneumonia gave 1 c.c. of "sterile pus."

2. A patient 14 years old. Puncture on the first day of pneumonia gave 1 c.c. of "pus."

3. Patient 18 years old. Puncture on the day before crisis, the seventeenth day, gave a "purulent exudate."

4. Patient 28 years old. On the fourth and sixth days puncture gave a "purulent exudate."

In all four cases the fluids were sterile by smears, cultures and inoculation.

5. Patient 15 years old. Puncture on the fourth day gave "pus" containing gram-positive, encapsulated, diplococci, which by inoculation were shown to be of very low virulence. All five cases recovered with spontaneous absorption.

Vaughan, Jr.,⁹ says that "Maragliano demonstrated serofibrinous or fibrinopurulent exudate in 65.5 per cent. of cases of typical pneumonia, by puncture. Marin found 41.5 per cent. of 978 cases at autopsy to have pleural fluid, and Kerr found in 178 autopsies 69 per cent. with fluids, 74 fibrinous, 38 serofibrinous and 6 acute purulent."

Levy¹⁰ mentions cases with fluid from the pleural cavities in pneumonia, bronchopneumonia and influenza, in which ten were serous and nine "purulent." Three of the serous fluids were free from organisms; the others all contained organisms. Unfortunately his data are very scanty.

Sauer,¹¹ in 1914, observed two cases in children, the only cases reported in children.

1. Four years old. The patient had pneumonia involving the lower and middle right lobes. Puncture two days before crisis gave a few drops of "pus" which contained gram-positive diplococci. The next day 7 c.c. of similar "creamy pus" was withdrawn. Gram-positive, encapsulated diplococci were shown by

8. Dumont and Mossy: Bull. et mém. Soc. d. hôp. de Paris, June 14, 1912; ref. Semaine méd., 1912, p. 299.

9. Vaughan, Jr.: Jour. Michigan State Med. Soc., 1914, xiii, 573.

10. Levy, E.: Arch. f. exper. Path. u. Pharmakol., 1890, xxvii, 369.

11. Sauer: Arch. Pediat., March, 1915, xxxii.

smears and cultures. By puncture six days after crisis no fluid was obtained. The patient recovered, the fluid being spontaneously absorbed.

2. Patient 3 years old. Puncture was made on the fifth day and 0.5 c.c. of "pus" aspirated. It contained leukocytes but no organisms. Cultures were sterile. On the following day there could be heard on deep inspiration, a friction rub. The patient recovered.

AUTHOR'S CASES

In a series of fifteen cases of typical lobarpneumonia or bronchopneumonia, in children under 4 years of age, seen in The Children's Memorial Hospital during January, February and March, exploratory punctures of the chest were made as early as possible in the course of the disease. The needle was put in over the area of greatest impairment as shown by physical signs and roentgenograms. In only one of the cases where fluid was not found at the first puncture, were subsequent trials made, and no fluid was found until the twenty-second day, when a typical metapneumonic empyema was found.

In six of these fifteen cases (40 per cent.) fluid was recovered by puncture before the seventh day of the disease, always before the crisis. Five of the six fluids were opaque and yielded a large clot. They contained a large number of cells, between 70 and 80 per cent. polymorphonuclear leukocytes. No micro-organisms could be demonstrated in them by smears. Cultures on agar, milk, bouillon, and with some on blood-agar, gave no growths. Inoculations into mice were without harmful results, except in one case in which the mouse died within twenty-four hours, but no lesions were found and no organisms could be grown from its heart's blood or serous cavities. In all five cases the fluids were absorbed spontaneously, as was shown by later punctures and roentgenograms. The clinical course of the disease was never noticeably affected by the presence of these fluids.

In one case two days after fluid had been found the patient died from other causes than the pneumonia. The autopsy showed no fluid in the pleural cavity. There were several large areas of bronchopneumonia. Over one of these areas, in about the region where puncture had been made and fluid obtained, the pleural surface was somewhat dulled and showed a thin, very fresh, slight deposit of fibrin.

In the sixth case, on the second day of the disease, about 5 c.c. of purulent fluid was removed by puncture. It was opaque, did not coagulate, but on standing separated into a heavy sediment and a semiopaque supernatant fluid. It contained many polymorphonuclear cells and also cocci in diplo- and double-chain form. On all ordinary mediums cultures grew well. Inoculation of 1 c.c. into the peritoneal cavity of a mouse caused death in less than twenty-four hours, the organism being recovered from its blood and serous cavities. The group of pneumococci to which this organism belonged was not determined.

The patient was operated on and the pleural cavity freely drained, but death occurred in a few days. No necropsy was obtained.

In brief the histories of these cases follow:

CASE 1.—Peter O., aged 6 months, was admitted to the hospital January 1. His mother was at that time in a hospital with pneumonia. Birth and previous history negative. Breast fed until the onset of mother's illness.

Present Illness.—For two weeks preceding admission there was coughing, restlessness and loss of appetite, slight diarrhea and loss of weight.

Examination.—On admission examination showed a well nourished, well developed, rachitic baby boy. Occasional cough. Chest symmetrical, expansion good, respiration neither rapid nor labored. Percussion note of normal relative intensity over entire chest. There was no tubular breathing anywhere, but a few moist râles in the interscapular region. Otherwise negative.

On the third day in the hospital, January 3, cough continued. Respirations somewhat increased in rate. Lungs: Anteriorly no dulness, no râles, no bronchial breathing. Over the left lower back percussion note slightly high pitched, many medium moist râles and a few large dry râles. Occasional râles over the right back. White blood cells 26,000.

Roentgenogram of Chest: A rather broad mediastinal shadow and rather profuse, though not intense mottling throughout both lungs—about the same on both sides.

Von Pirquet test negative.

January 6, marked dulness at the left base with distant tubular breathing. A needle was put into the left pleural cavity in the sixth interspace and 5 c.c. of fluid drawn off. This fluid was thin, cloudy and coagulated. Smears showed large numbers of leukocytes, but no organisms. Cultures gave no growth.

January 7. Roentgen ray showed a shadow at the left base.

January 8. Dulness still present at the left base with distinct tubular breathing. A needle was put into the pleural cavity near the point of previous puncture. Only a few drops of fluid could be obtained. Sterile as previously.

January 11. Dulness as before. Roentgen-ray shadow at left base of same density as on former exposure.

January 15. Dulness less marked. No more tubular breathing. Crisp crepitant râles.

January 23. Roentgen examination: Chest clear. Other signs returning to normal. From this time on the chest remained normal.

CASE 2.—Harriet J., aged 6 months, admitted to the hospital in October, 1914, with bronchitis and nutritional disturbances. Family history unimportant.

Previous History.—Birth normal. Had never been strong. Always had gastro-intestinal disturbances, and one convulsion.

Examination.—Showed a poorly nourished baby girl. Dec. 25, 1914, the lungs were clear.

Jan. 12, 1915. Patient had been coughing for several days. Throat rather red. Chest: no dulness on percussion, no tubular breathing, but diffuse coarse, moist râles.

January 13. High pitched moist râles over left back.

January 18. Over the left base quite marked impairment of the percussion note. Breath sounds over this area faintly tubular. Many râles throughout both lungs.

A needle was put into the pleural cavity in the seventh interspace at the angle of the scapula and about 1 c.c. of thin cloudy fluid, which coagulated, was obtained. Smears showed many pus cells; no micro-organisms. Cultures gave no growth. Injection of 0.75 c.c. into the peritoneal cavity of a mouse caused no appreciable result.

January 19. Marked dulness at the left base and distinctly tubular breath sounds.

January 20. Patient died. Immediately after death a needle was put in the chest at about the point of first puncture, but only a few drops of fluid were obtained. This was found sterile by smears and cultures.

Note at Necropsy (Dr. Riley).—On opening the chest there was no free fluid in the pleural cavities and no adhesions. Over the left lower lobe was a slight, sticky, thin fluid. The left lung showed nodules of bronchopneumonia in posterior portion of upper lobe and much consolidation of the paravertebral portion of lower lobe. Over this region the pleural surface was slightly dulled by a thin fibrinous exudate.

CASE 3.—Harold Mc., aged 4 years, admitted to the hospital Jan. 22, 1915. Family history unimportant. Previous history negative.

Present Illness.—This began five days before admission, with cough, fever and vomiting.

Examination.—On admission examination showed a well developed, well nourished child. Respirations rapid with expiratory grunt. On percussion there was marked dulness from the third left interspace in the axilla to the base of the lung posteriorly and anteriorly. Over this area were crepitant and subcrepitant râles and bronchial breathing. Remainder of the lungs normal. White blood cells 34,000. Polymorphonuclears 92 per cent.

January 23.—Roentgen examination of chest showed uniform dulness at the left base below the seventh space.

January 24.—Dulness over left back with distant tubular breathing. A needle was put into the thoracic cavity in the ninth interspace below the angle of the scapula and 5 c.c. of greenish-yellow, viscid fluid obtained. It coagulated quickly after removal. Polymorphonuclears 66 per cent. No organisms in smears: cultures gave no growth; 1 c.c. injected into a mouse gave no results.

January 25. Area still dull. Bronchial breathing has disappeared. White blood cells 27,000.

January 27. By puncture 0.5 c.c. of bloody fluid was obtained. It was sterile.

January 29. Impairment less marked. Many râles, but no tubular breathing. Roentgen-ray examination of chest showed shadow over entire lower left.

January 30.—Temperature now continually normal.

February 2.—Patient has entirely recovered. Dulness has disappeared.

CASE 4.—Edwin Z., aged 17 months. Admitted to hospital January 31. Family and previous history not remarkable.

Present Illness.—This began one week before admission, with diarrhea, cough, fever, loss of appetite and vomiting.

Examination.—This showed a well-nourished boy, coughing much. Chest symmetrical; respirations accelerated but not labored. Dulness on percussion over the right back and axilla. Fine high-pitched râles, tubular, diminished breath sounds. Remainder of lungs normal. White blood cells 16,000.

February 2. Puncture made at two points below the right scapular; 1.5 c.c. of bloody, serous fluid, which coagulated, was obtained. Smears showed no organisms. Cultures remained sterile. One c.c. injected into the peritoneal cavity of a mouse was followed by death in twenty-four hours. No lesion of organs. No cultures obtainable from blood or serous cavities.

February 3.—Roentgen-ray examination of chest showed slight dulness at the right base below the angle of the scapula.

February 7. Puncture made but no fluid could be obtained.

February 12. Patient in good condition, left the hospital.

CASE 5.—Thomas M., aged 9 months, admitted to hospital March 31. Family history unimportant. Previous health good until last two months.

Present Illness.—This started six weeks before admission with fever, cough, vomiting and diarrhea.

No.	Name	Age Months	Clinical Diagnosis	Admit- ted	Date of Explor- atory Puncture	Probable Day of Disease of Puncture	Amount c.c.	Type of Fluid	Cultures	Animal Inoculation
1	Peter O.	6	Lobar pneumonia, enteritis, otitis media	1/ 1/15	1. 1/ 6/15 2. 1/ 8/15	Fourth Sixth	5 1	Turbid; slightly coagulating; containing many pus cells; no bac- teria.	No growth on agar, milk, or bouillon.
2	Harriet J.	6	Bronchitis, broncho- pneumonia, enteritis	11/27/14	1. 1/18/15 2. 1/20/15	Sixth Eighth (post- mortem)	1 †	Thin, cloudy, coagulating; many pus cells; no bac- teria.	No growth on ordi- nary me- diums.	0.75 c.c. into peritoneal cav- ity of a mouse; no develop- ments.
3	Harold McM.	48	Lobar pneumonia	1/22/15	1. 1/24/15 2. 1/27/15	Sixth Ninth	5 0.5	Green, yellow, viscid, coagu- lating; many cells; 62 per cent. P. M. N.; no bacteria.	No growths	1 c.c. into peri- toneal cavity of a mouse; no developments.
4	Edwin Z.	17	Lobar pneumonia	1/31/15	1. 2/ 2/15 2. 2/ 7/15	Fourth Ninth	1.5 0	Blood stained serous fluid; coagulating; no bacteria.	No growth	1 c.c. into peri- toneal cavity of mouse; death in 24 hours; no lesions; no bac- teria from heart's blood or peritoneum.
5	Thomas N.	9	Lobar pneumonia, empyema	3/31/15	1. 3/31/15 2. 4/ 1/15 3. 4/ 2/15 4. 4/ 5/15 5. 4/ 6/15*	Fourth Fifth Sixth Ninth Tenth	3 2 0 2 0	Thin cloudy, coagulating; many pus cells; no bac- teria; (4) bloody.	No growth on agar, blood agar, milk, broth	
6	Lena B.	9	Broncho- pneumonia, empyema	3/ 9/15	1. 3/11/15 2. 3/12/15 3. 3/13/15 Operation	Fourth Fifth Sixth	5 †	Thin pus; creamy pus; not coagulat- ing; cocci in diplo- and chain form.	Profuse growth on agar and in milk and bouil- lon	1 c.c. into peri- toneal cavity of mouse; death in 20 hours; cocci recovered from heart's blood and ser- ous cavities.

* Alboline injected. † Few drops. ‡ Very much.

TABLE 3.—PNEUMONIA CASES WITHOUT PLEURAL FLUID

No.	Name	Age Years	Clinical Diagnosis	Date Admitted	Date of Explora- tory Puncture	Probable Day of Disease of Puncture	Amount c.c.	Character of Fluid	Cultures
7	Maurice C.	5	Lobar pneumonia; empyema	1/13/15	1. 1/18/15 2. 1/24/15 3. 2/ 2/15 4. 2/ 4/15 5. Oper- ation	7 13 22 24 25	* 0 30 5 ++	B l o o d stained Creamy pus Streptococci Creamy pus Streptococci Creamy pus Streptococci	No growth Streptococci Streptococci Streptococci
8	Eleanor F.	2	Lobar pneumonia	1/15/15	1/17/15	..	†	B l o o d stained; no organ- isms	No growth
9	Marie O.	3	Lobar pneumonia	2/ 6/15	2/ 7/15	7	0
10	Chessie R.	1½	Bronchopneumonia	2/25/15	2/26/15	4	†	B l o o d stained; no organ- isms	No growth
11	Dorothy F.	2	Lobar pneumonia	2/ 6/15	2/12/15	..	0
12	Herman G.	2½	Bronchopneumonia	2/24/15	2/26/15	5	0
13	Kosta P.	2	Lobar pneumonia	3/16/15	3/17/15	5 (?)	0
14	John O.	3	Bronchopneumonia	3/16/15	3/19/15	6	0
15	Helen C.	6	Lobar pneumonia	3/23/15	3/27/15	6	0

* Few drops. † Less than 1 c.c.

TABLE 4.—SUMMARY OF CASES BY VARIOUS AUTHORS

Collected by	No. Cases	Type of Fluid	Amount of Fluid c.c.	Cultures	Results	Ages
Siems	26	Serous 9 Sero-fibrinous 11 Purulent 4	A few drops to 700	Sterile, 14; pneumococci, 8	Recovered, 18; Died, 8	All adults
Widal	2	Seropurulent (?)	5 and 100	Sterile	Recovered	24 years 34 years
Pende	3	Purulent fluid	Sterile	Recovered	13 years 14 years 15 years
Dumont	3	"Pus" 2 (?)	20 to 40	Sterile	Recovered	26 years 52 years 24 years
Gerhardt	5	Pus and purulent fluid (?)	0.5 to 5	4 sterile; 1 pneumococci	Recovered	26 years 14 years 18 years 28 years 15 years
Sauer	2	Pus (?) Pus	1	1 sterile; 1 pneumococci	Recovered	4 years 3 years
Gerdine	6	Serous or seropurulent Pus 1	1 to 5	5 sterile; 1 pneumococci	Recovered, 4; Died, 2 *	6 months 6 months 9 months 9 months 17 months 4 years

* Death due to other complications in one case.

Examination.—On admission examination showed a well nourished, well developed baby, very ill. Respiration rapid. Dulness, suppressed breath sounds and many medium, moist râles over lower left back.

March 31. A puncture was made over the lower left lobe and about 3 c.c. of thin turbid coagulating fluid was obtained. Smears showed no organisms. Cultures gave no growth. Animal inoculation with no results.

April 1. Puncture over left base 2 c.c. of thin blood-stained sterile pus obtained.

April 4. Dulness less over left base. Breath sounds clearer. No fluid obtained by puncture.

April 5. Dulness more marked. Puncture gave 2 c.c. of very bloody fluid. Sterile as before. April 6. Puncture. No fluid could be found. The patient recovered.

CASE 6.—Lena B., aged 9 months, admitted March 9, 1915. Family history and previous history unimportant.

Present Illness.—This started the day before admission, with vomiting.

Examination.—On admission examination showed a well nourished, well developed baby. Chest dulness over left side and lower lobe in back. Bronchial,

distant breath sounds over area of impairment. Moist râles over entire side. Right lung normal. White blood cells 14,900.

March 11. Puncture made at angle of left scapula and 5 c.c. of true pus separating into layers without coagulation, were removed. Smears showed leukocytes, endothelial cells and cocci in groups, double chains and pairs. Cells 40,000 per c.mm. Cultures showed rapid growths.

Roentgen-ray examination of chest showed on the entire left side a uniform shadow.

March 12. Dulness over left side more marked.

Puncture made; 6.5 c.c. fluid removed. It was exactly as that of the previous day. One c.c. injected into the peritoneal cavity of a mouse was followed by death in less than twenty hours. Cultures from the heart's blood and serous cavities of the mouse showed the same organism in pure culture as obtained from the pus from the baby's chest.

Roentgenogram showed shadow of entire chest on left side.

March 13. The chest opened and pus evacuated at operation (Dr. Buford). Pus continued to discharge through drainage tube during next four days.

March 17. Patient died. No necropsy obtainable.

Tables 2 and 3 summarize the findings in my series of cases.

Table 4 shows the findings in all cases reported, including my group.

Table 5 shows the grouping according to the nature of the fluids and the bacteriologic findings.

TABLE 5.—GROUPING ACCORDING TO NATURE OF FLUID AND BACTERIOLOGIC FINDINGS

Total number of cases collected.....	47	Cultures made in.....	42
Definitely serous or serofibrinous.....	28	Pneumococci	4
		(Death in 3)	
		Sterile	22
Definitely purulent or seropurulent.....	4	Pneumococci	3
		Sterile	1
Without sufficient description indefinitely		Pneumococci	3
"purulent"	13	Sterile	10
No puncture (physical signs)	2		

In many of the cases reported the description of the fluids obtained are not sufficient to determine their exact nature. They are called "seropurulent," "purulent fluids," "purulent exudate," and "pus," or are mentioned as "cloudy," "opaque" or "rich in pus globules," while others are "cloudy fluids which are apparently seropurulent." Many times the fluids are said to be "very rich in fibrin." It would seem that these fluids are probably similar to some of ours, which, though cloudy and containing many pus cells, were not true pus, since there was definite coagulation. In some instances fibrin deposits took place in the pleural cavity, as was shown by one case at necropsy (this series), and suggested in another case (Sauer) by the presence of a friction rub on the day after fluid had been found. In some cases, however, there was no coagulation, the fluid dividing into a cellular sediment and liquid serum.

For the formation of pus two conditions are necessary according to Opie;¹² the accumulation of leukocytes and the necrosis and liquefaction of cells and tissue elements. Pus consists of: (1) the constituents of the exuded blood plasma; (2) the constituents of leukocytes and tissue cells that exist free in the pus; (3) the products of digestion of the proteins of the leukocytes and necrosed tissues. It divides into two chief parts, pus corpuscles and pus serum. This pus serum differs from blood serum chiefly in the substances added to it through the proteolytic changes that occur in pus, and also in that it has lost its antiproteolytic property, containing instead free leukoprotease. The fibrinogen that escapes from the vessels into suppurating areas becomes so altered that pus will not coagulate even on the addition of fibrin ferment.

In the majority of cases where the fluids were serofibrinous, they were free from bacteria in smears, by cultures and by animal inoculation (for instance, in 14 of 20 cases from Siems). In the cases in which the description permits us to speak of truly purulent exudate (four in all) micro-organisms were found in three. There remain a number of cases (thirteen) in ten of which the fluids designated as seropurulent or purulent were found sterile. The descriptions of these fluids are not sufficiently detailed to determine whether they were real pus or not. It is probable that in some of these cases an actual purulent exudate was present in spite of the negative bacteriologic findings. From the available data it would seem where we are dealing with frankly purulent fluids, micro-organisms are likely to be present. This is in contradiction to the statement made by Gerhardt, for instance, who, like others, seems to regard the absence of micro-organisms more or less characteristic of the "parapneumonic empyema." The frequency or rarity with which micro-organisms are present in such empyema can not be decided at present, but we have sufficient data to warrant the statement that the absence of bacteria certainly cannot be regarded as characteristic of this complication of pneumonia. It is reasonable to suppose that the fluids will show a gradual transition from serous to purulent. If no organisms are present in the pleural cavity, the fluid may remain serous or serofibrinous with few or many leukocytes, whereas the presence of organisms may lead to the formation of pus. So when a purulent exudate is found, it is probable that in the majority of these cases organisms have been present at one time or another.

The organisms were not always of a high grade of virulence, as shown by animal inoculation. This difference in virulence of the

12. Opie, *Inflammation*, Arch. Int. Med., 1910, v, 541; and *Jour. Exper. Med.*, 1903, ix.

organisms may be of use in prognosis. A possibility of error must be kept in mind. The introduction of this foreign fluid into the peritoneal cavity may kill the mouse, as in one of our cases. The mouse died in twenty-four hours, but no lesions were found and no organisms could be grown from the heart's blood or serous cavities. In the cases where death of the mouse occurred in a short period and with inoculation of small amounts of fluid, the patient also died; while when the animal survived, the patient recovered and the fluid was absorbed spontaneously. It is evident, therefore, that the cases in which a real parapneumonic empyema occurs need not all be of a benign type as Gerhardt claims.

This is of further importance in its bearing on the treatment of these cases. Since the serous fluids and the purulent ones in which the organisms are of low grade virulence are, as a rule, spontaneously absorbed, surgical interference is not needed unless the amount is so large as to cause discomfort. On the contrary, where organisms of high grade virulence are found, surgical treatment may perhaps enter into consideration.

Although the literature on this subject seems large, we feel that the actual number of cases with sufficient description of the fluid found is too small for very definite deductions. However, we may put forward tentatively the following conclusions:

CONCLUSIONS

1. Fluid is present in the pleural cavity in a large number of cases of pneumonia before the crisis and can be demonstrated, sometimes by physical signs, sometimes by Roentgen ray, and by puncture, even when other physical signs are not apparent.
2. The clinical course of the pneumonia may not be altered by this complication.
3. In the majority of cases the fluid is serofibrinous in character, though perhaps containing a large cellular element, polymorphonuclear in type. These fluids are sterile as a rule.
4. True pus is present much more rarely and may contain organisms of more or less virulence. The frequency of the presence of organisms in these cases cannot be decided on the data as yet secured.
5. The virulence of the isolated organisms determined by animal inoculation seems to be of value in prognosis.
6. Only in cases with serofibrinous and purulent fluids containing organisms of a high grade of virulence should surgical interference enter into consideration.

THE NUTRITIVE VALUE OF BOILED MILK *

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The experimental work involved in this report is the result of an attempt to determine the comparative nutritive efficiency of milk heated to different temperatures. There is considerable evidence in the literature to the effect that scurvy among infants may be caused by feeding cooked milk exclusively; in fact, this notion is so prevalent that many pediatricists still insist on giving raw cow's milk, notwithstanding that the hygienic conditions of this may be far from desirable. It is only in our larger cities that certified milk may be obtained, and even here the price makes it prohibitive for the great majority of homes.

In order to meet present conditions and to make milk more nearly safe for infant feeding, the practice of pasteurizing or boiling has been resorted to. Pediatricists differ as to the relative value of these two processes. The European pediatricists¹ report excellent results with boiled milk—the time of boiling varying within comparatively wide limits. The American pediatricists, on the other hand, have favored the pasteurization process. However, the fact that casein curds sometimes found in the stools of infants fed either raw or pasteurized cow's milk are almost unknown in the European clinics, leads us to believe that boiled cow's milk may be better digested by infants than raw or pasteurized. This assumption is further borne out by the work of Brenneman,² who has shown that the clot formed from boiled cow's milk during gastric digestion more nearly resembles the clot formed during the digestion of woman's milk. It is much finer than that formed from raw milk, thus making for more complete digestion and absorption further on in the digestive tract. But conclusive experimental evidence as to the relative nutritive value of raw and cooked milk is lacking, owing to the fact that the experiments with animals have been continued for too short a time, and in the case of

* Submitted for publication Oct. 19, 1915.

* From the Department of Home Economics, University of Wisconsin.

1. The literature has been reviewed by Lane-Clayton. Report to the Local Government Board, London. New Series, 1912, No. 63.

2. Brenneman, J.: Jour. Am. Med. Assn., 1913, lx, 575.

babies, other substances, such as cereal waters, or various fruit juices have been superimposed on the basal diet. Furthermore, in many cases, the records leave one in doubt as to just what is meant by boiling. It is conceivable that milk brought just to the temperature of 100 C. is less changed chemically than that sustained at this temperature for a considerable period. The importance of knowing more definitely regarding the nutritive efficiency of pasteurized milk and milk boiled for different lengths of time, is obvious.

PLAN OF INVESTIGATION

In our investigation, rats just past the suckling period were fed milk boiled one minute, five minutes, and forty-five minutes, respectively. Other rats were fed pasteurized milk³ and one group was given milk heated in an autoclave to a temperature of 114 C. for forty-five minutes. Rats on raw milk were used as controls. In each case, the milk was supplied *ad libitum*; as soon as the containers were emptied, these were refilled. During our preliminary trials, the experimental animals were given daily in addition to the milk, 10 gm. of a cooked cornstarch-agar-agar mixture, consisting of 15 per cent. cornstarch, 2 per cent. agar-agar, and 83 per cent. water. But since later work showed that defecation took place normally in the absence of this, it was discontinued.

RESULTS OF EXPERIMENTS

The growth curves of all animals fed milk boiled one minute and ten minutes, respectively, are surprisingly uniform (Charts 1 and 2). In no case, however, do these conform to the normal growth curves as given by Osborne and Mendel and McCollum and Davis. During the first six weeks of the diet, growth was apparently normal. From this time on, the weight curves show little or no gain. The curve of growth of those animals fed milk boiled forty-five minutes (Charts 2 and 3) show considerable variation; none of these, however, is in accord with the normal growth curve. This variation, we believe, is explained by the fact that during the early part of the investigation we had some difficulty in keeping the rats from killing one another. On several occasions, small portions of the dead animals were eaten. Those animals (Chart 5) fed milk heated during forty-five minutes at 114 C. grew for a short time at about the same rate as those animals given milk heated to the lower temperature. Nutritive disaster, however, was much more sudden. All animals fed this diet exclusively, died within eleven weeks of the beginning of the experiment, whereas

3. The process involved consisted in heating the milk to 83 C. by passing it over heated drums and then cooling it immediately.

the animals which received milk heated only to the boiling point lived many months. But what is even more significant than the slow growth, is the fact that we never had reproduction with any of our experimental animals fed boiled milk, although many were long past the period of sexual maturity, and in many cases, their weight was greater than our normal animals which were reproducing.

The value of raw milk as a food which meets all the nutritive requirements for growth and reproduction has been shown by various investigators. McCollum⁴ fed a pig for a period of 395 days on raw cow's milk. It grew from a 23-pound animal to one weighing 406 pounds. During this time the sow gave birth to two dead and eight living young, each weighing from 2 to 3 pounds. The latter were suc-

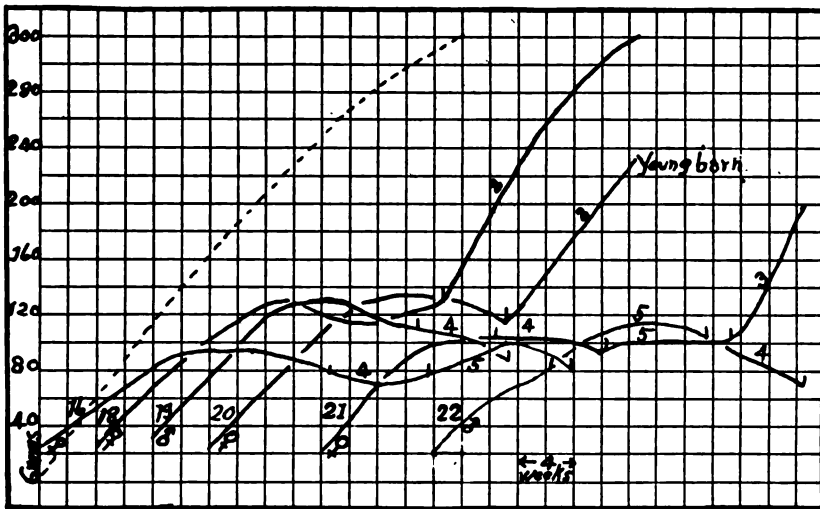


Chart 1.—Curves of growth of rats fed milk boiled one minute. Rats 18 and 20 (Period 2) show the influence of the addition of small amounts of egg to the diet. The addition of casein from boiled milk also caused growth to be resumed. (Rat 21, Period 3). The addition of neither 6.5 per cent. sucrose (Rats 16, 19, 21 and 22, Period 4), nor of dextrimaltose (Rats 16, 21 and 22, Period 5), caused an appreciable increase in weight. The curve of normal growth is represented by the broken line.

cessfully suckled. Osborne and Mendel⁵ state that in their "numerous experiments milk has proved to be an adequate food both for growth and maintenance. Young rats fed solely on a milk food which we have been accustomed to use, not only have grown from infancy to full maturity, but have also given birth to litters of normal young. . . . One must conclude from these facts that the milk food con-

4. Henry: Feeds and Feeding, 1912, p. 98.

5. Osborne and Mendel: Jour. Biol. Chem., 1913, xv, 313.

tains all that is essential for both growth and maintenance." The milk food referred to consists of a mixture of milk powder, starch, and lard. We infer that in these experiments in which the authors state that milk has proved to be an adequate food, milk powder was used. Wheeler⁶ reports normal growth over a period of sixty

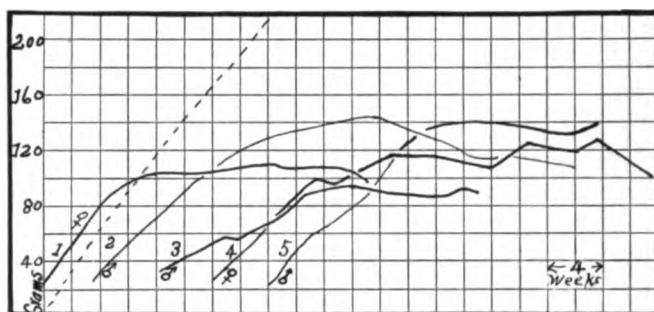


Chart 2.—Curves of growth of rats fed milk heated to 100 C. during ten minutes. The curve of normal growth is represented by the broken line.

days in mice fed raw cow's milk to which was added 6.5 per cent. sucrose. There are no records of reproduction with these mice, but we have no reason to doubt that, had the experiment continued longer, this would have taken place:

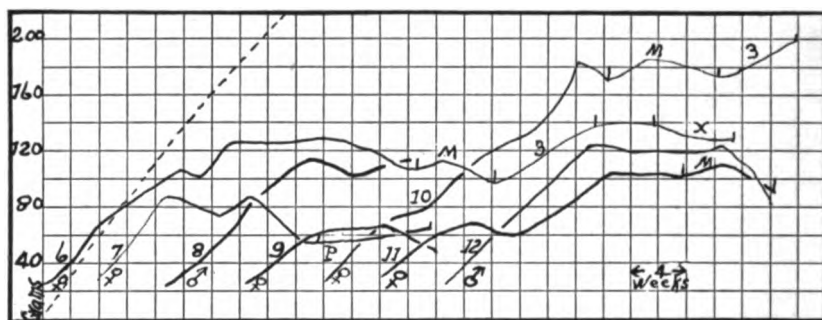


Chart 3.—Curves of growth of rats fed milk boiled forty-five minutes. The addition of casein from boiled milk caused growth to be resumed (Rats 6 and 10, Period 3). Pasteurized milk caused no improvement in Rat 7 (Period P). The addition of 6.5 per cent. lactose to the diet of boiled milk caused a slight increase in weight (Rats 8, 10 and 11, Period M), followed by a decline. The addition of meat extract to the boiled milk caused no gain in Rat 8, Period X). The curve of normal growth is represented by the broken line.

Up to the present we have been unsuccessful in our attempts to feed rats for any length of time on either raw or pasteurized cow's milk alone. Growth on raw milk took place much more slowly during

6. Wheeler, Ruth: *AM. JOUR. DIS. CHILD.*, 1915, ix, 300.

the early part of the growth period than with either boiled or pasteurized milk; in fact, we have been unable to keep rats alive on this diet. Three of a group of six on raw milk exclusively, died. Two others, apparently doomed, were given very small amounts of other food material—eggs, toast, fruit, etc.—in addition to the raw milk. Normal growth was at once resumed. Other rats fed raw milk to which was

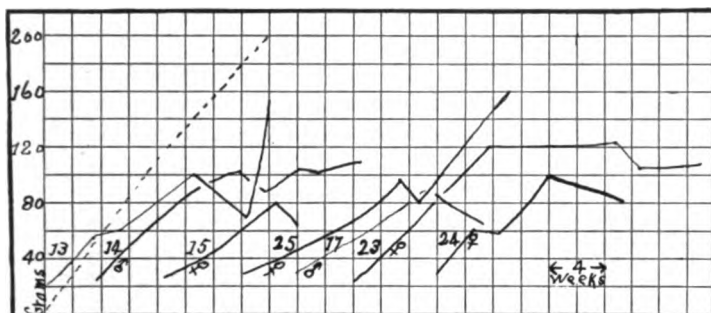


Chart 4.—Curves of growth of rats fed milk boiled forty-five minutes. The addition of well-washed egg yolk to the boiled milk diet caused growth to be resumed in Rats 13 and 25. The curve of normal growth is represented by the broken line.

added daily a small amount of beef extract (0.3 gm. per rat) grew at the normal rate (Chart 8, Rats 70, 72, 73, 74). Rat 71, the only female of the group, received raw milk for four weeks. During the third week there was no gain. Beef extract was then added to the diet; growth was at once resumed, and four weeks later this animal gave

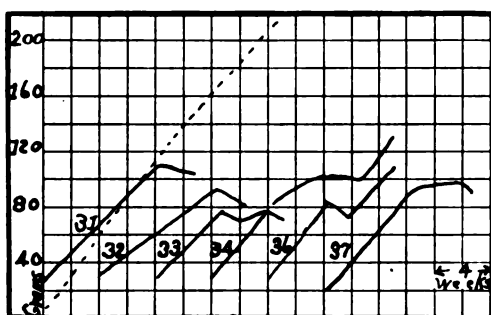


Chart 5.—Curves of growth of rats fed milk heated to 114 C. during forty-five minutes. The addition of egg yolk to the diet of Rat 36, and egg white to the diet of Rat 34, caused growth to be resumed. The curve of normal growth is represented by the broken line.

birth to two living young. These were successfully suckled. For three weeks following the weaning period two rats (Chart 7, Rats 64 and 65) were given raw milk plus small amounts of meat extract.

These were then transferred to the untreated raw milk diet and continued to grow at the normal rate for about four weeks. Following this, there was a decline in weight. Another raw milk animal (Chart 7, Rat 63) which was about to die, was given a mixed diet for three days and then returned to raw milk. Growth was at once resumed.

Those animals on pasteurized milk grew normally for about five weeks and then began to lose weight. Four died. Four others (Chart 6, Rats 42, 43, 44, 46) which were in the same moribund condition as those which died, were given small amounts of meat extract (0.3 gm. per rat) added to the pasteurized milk. Recovery followed and the animals continued to grow at the normal rate during the time of the investigation period.

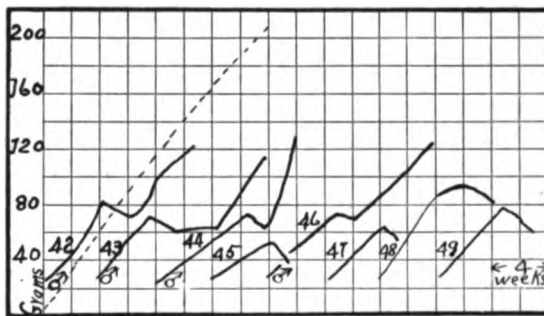


Chart 6.—Curves of growth of rats fed pasteurized milk. The addition of meat extract caused growth to be resumed. (Rats 42, 43, 44 and 46.) The curve of normal growth is represented by the broken line.

DISCUSSION OF RESULTS

We appreciate that criticism may be made to the effect that our animals were not kept under strictly aseptic conditions and that our failure to raise rats on either raw or pasteurized milk exclusively may be due to bacterial invasion. The results cited above, however, show that such cannot be the case, for all of our animals were kept under the same conditions. Apparently raw cow's milk is not well borne by young rats. By boiling, the milk has been made more digestible, but at the same time it has been chemically so changed as to render it an inadequate food. These results are comparable with those of other investigators who have shown that boiled milk of another species may be better borne than raw milk of another species. The milk powder used by Osborne and Mendel was apparently in such form as to be easily digested.

The part played by the beef extract in increasing the nutritive efficiency of raw and pasteurized milk is not clear. Obviously, the

increase in weight of our animals is much more than can be accounted for by the increase in the calorie value of the food ingested. Furthermore, the addition of the same amount of the extract to boiled milk caused no increase in weight during the brief experimental period—two weeks (Chart 3, Rat 8). It is well known that this material contains measurable amounts of amino-acids and inorganic salts, as well as very small quantities of soluble proteins, and the so-called extractives of muscle. But we can hardly believe that milk is deficient in those amino-acids essential for growth; nor can we think that the inorganic material is insufficient, since such noteworthy results⁷ have been obtained in investigations in which the mineral content of the food has been similar to that of milk. It is probable that the explana-

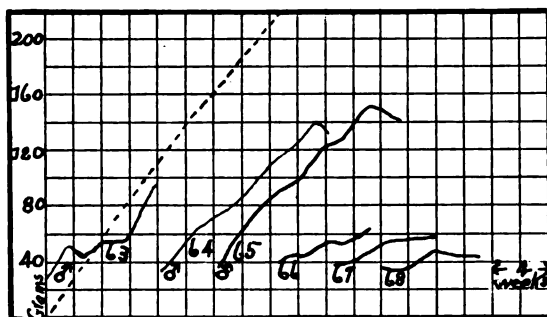


Chart 7.—Curves of growth of rats fed raw milk. Rats 64 and 65 received raw milk plus small amounts of beef extract during the first five weeks. From this time raw milk only was given. Rats 63 and 66 received a mixed diet for three days following a raw milk diet; the raw milk diet was then resumed.

tion lies in the well-known fact that the extractives of meat increase the digestive secretions, more particularly the gastric juice, and that both the raw and pasteurized milk have been made thereby more available. Experiments now in progress in this laboratory are aimed to determine this point. In the meantime, one is led to speculate as to what would be the effect of adding small amounts of meat extract to the diet of infants who are having difficulties in digesting raw cow's milk.

The failure of our rats to grow normally and reproduce when fed milk heated to a temperature of 100 C. or over, is undoubtedly due to the destruction, at least in part, of one or more of the essential constituents of milk. There is considerable evidence that high temperatures bring about definite chemical changes in the proteins of the milk.

7. McCollum and Davis: Jour. Biol. Chem., 1913, xv, 167.

Rettger⁸ found that on heating milk above 85 C. a partial decomposition of milk protein occurs, resulting in the liberation of volatile sulphid. Earlier work by Schulz⁹ showing that one of the sulphur cleavage products of albumin, namely, cystin, gave off only part of its sulphur by boiling with alkali, suggests that in the process of heating milk some of the cystin is destroyed. It is possible that the chief protein of milk is somewhat deficient in this essential amino-acid; when some of this is destroyed by heating, there is too little left to furnish the adequate amount for growth and reproduction. This theorem is further enhanced by the work of Osborne and Mendel.¹⁰ These investigators have shown that rats can be maintained on a very much smaller amount of casein as the sole protein in an otherwise adequate diet if cystin is added. Our experience seems to bear this out. Two rats (Chart 1, Rats 19 and 20) which had ceased to grow on milk boiled one minute, were given daily in addition to the regular diet 13

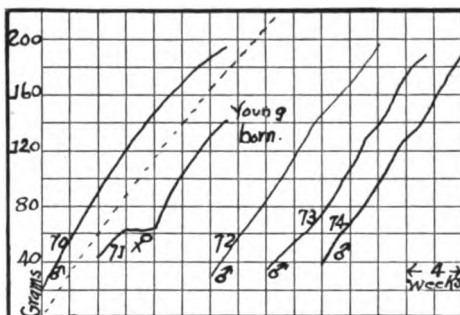


Chart 8.—Curves of growth of rats fed raw milk. Rat 71 received raw milk for four weeks following the weaning period; from this time a small amount of beef extract was added daily to the raw milk. Rats 70, 72 and 73 received raw milk and beef extract during the entire experimental period.

gm. of hard cooked egg. Within a very few days there was a marked improvement in appearance. Rapid growth then followed and the female, two months later, gave birth to a litter of eleven young. Hard cooked egg yolk, from which all soluble material had been removed by repeated washing, was as efficient as the whole egg in correcting the deficiency of heated milk (Chart 4, Rats 14 and 25). The addition of casein, precipitated from boiled milk and having a protein content equivalent to nearly twice that supplied by the egg, also caused growth to be resumed (Chart 3, Rats 6 and 10; Chart 1, Rat 21). Up to

8. Rettger: *Am. Jour. Physiol.*, 1902, vi, 450.

9. Schulz: *Ztschr. f. physiol. Chem.*, 1898, xxv, 16.

10. Osborne and Mendel: *Jour. Biol. Chem.*, 1915, xx, 351.

the present time—eight weeks after the beginning of the casein diet—we have had no reproduction in these rats. It appears, therefore, that the protein of egg is more efficient as a corrective of the defects of heated milk than is an increased amount of casein. Nevertheless, we must not fail to appreciate that there may be other contributing factors, such as the inorganic materials, growth determinants, etc., present in the egg yolk or present in larger proportions than in the casein. The practice among some pediatricists of feeding babies with boiled or pasteurized milk mixtures having a higher protein content than is usual for raw milk feeding, is noteworthy in this connection. Also the practice of introducing egg yolk into the diet of infants fed on cooked cow's milk at an earlier age than those fed on mother's milk, is apparently justified.

The increase in weight in our animals to which small amounts of egg, in some cases, and casein in others, were added, might seem to be explained by the increase in the caloric value of the food ingested. Experiments aimed to determine this point were tried. To the diet of rats fed boiled milk was added 6.5 per cent. sucrose, 6.5 per cent. lactose, and 6.5 per cent. dextrimaltose, respectively. The very slight and not well sustained increase in some cases (Charts 1 and 3, Rats 16, 18, 8, 10 and 11) and the lack of increase in others (Charts 1 and 3, Rats 19, 21 and 22) show that this cannot be the explanation. Moreover, the fact that rats can grow normally and reproduce on raw milk to which small amounts of meat extract are added, indicates that the animals are able to ingest enough milk to fulfil physiologic requirements.

SUMMARY

Our results point to the conclusion that milk heated to the boiling temperature or thereabouts is an inadequate food. Rats fed on boiled milk grew to about half their normal size. Although we have been able to keep these experimental animals for many months on boiled milk, in no case have we got reproduction, nor have any of our animals reached the normal weight for adult rats.

Milk which is kept at the boiling temperature for forty-five minutes is no less efficient as a food than milk boiled for much shorter periods—ten minutes or one minute. The chemical changes which make heated milk an inadequate food are brought about at the boiling temperature or thereabouts. The value of pasteurized milk as a food, therefore, will depend on the temperature to which it is heated during the pasteurization process. Heating milk to a higher temperature than boiling (114 C.) makes it even less valuable as a food.

Although boiled cow's milk is an inadequate food for rats, it is apparently better borne than raw or pasteurized cow's milk, for we have been unable to raise young rats on either exclusively. However, rats fed both raw and pasteurized milk to which small amounts of meat extract were added grew at the normal rate. The explanation of this lies, possibly, in the fact that the meat extract caused an increase in the digestive secretions, thus making the milk more available.

The advantage of using raw milk for infant feeding is obvious. When babies are unable to digest raw cow's milk, however, or there is danger that the milk may be contaminated, we believe that the pediatricist is justified in using boiled milk. When this is given, the mixture should have a higher protein content than when raw milk is used.

CONGENITAL SYPHILIS, SIMULATING MONGOLISM, IN ONE OF TWINS *

FRANK VAN DER BOGERT M.D.

SCHENECTADY, N. Y.

Recently three children were presented at the Children's Dispensary of Schenectady. Two were, to all outward appearances, of the Mongolian type. The third, a twin of the younger, apparently perfectly normal.

The father and mother are seemingly healthy Italians, not of the lowest class. There had been no miscarriages, but four children in all, the fourth said to be well. A history of syphilis in the parents was not obtainable.

The mother's age at the time of birth of the older child, now 9 years, was 18. The second, now 8, was born when the mother was 20. The twins, 5 years old, one normal, the other diseased, were born when she was 22.

These ages of the mother at the time the several births occurred are mentioned because mongolism is likely to show itself in the offspring of women of advanced age, of women who have borne many children, or of young women in whom the reproductive functions have not been fully developed.

The mother was neither old nor was she worn out by numerous pregnancies when the twins were born, but the first child showing evidence of the mongol, was born when she was comparatively young.

The similarity in appearance of some cases of congenital syphilis to mongolism has been suggested, though not very generally realized.

Still¹ says that in his experience the two conditions most commonly confused in the diagnosis of the mongol have been cretinism and congenital syphilis, and calls attention to the existence of snuffles and the flattened bridge of the nose in both the congenital syphilitic and the mongolian idiot.

About a year ago the two diseased children were shown before a clinical meeting and all present admitted them to be typical mongols. A careful study and physical examination of the diseased twin, however, leads one to believe that he is not a typical mongol.

At first sight the face is characteristic but on analysis of the features the broad, flattened nasal bridge is all that is distinctive. The palpebral fissure is narrow, but there is slight if any slanting. The mouth is held slightly open, but the tongue does not protrude. The tongue shows no distinct enlargement of papillae, nor is it fissured. The head is not flattened anteroposteriorly and the circumference is practically normal. There is no blepharitis, no heavy or

* Submitted for publication Nov. 1, 1915.

1. Still: Common Disorders and Diseases of Childhood, London, 1910.

snorting respiration. The hands are not characteristic of the mongol. The child gives a history of irregular teething and there is a slight heart lesion, but these conditions are not peculiar to the type.

As to his mental condition, he is said to be brighter than his apparently normal twin brother.

Conclusive evidence of syphilis is found in dwarfed stature, a large liver palpable 3 inches below costal margin, a spleen extending nearly to the crest of the ilium below and nearly to the navel in front, and a positive Wassermann.

During the examination an interesting condition of the fingers was noted, the cuticle merging with the dorsal surface of the nails with no line of demarcation at the junction. This condition was not present on the toes.



Twins reported on by author, showing difference in development and mongolian features of smaller.

The blood showed, Oct. 4, 1915, reds, 2,680,000; whites, 10,200. I quote from the report on the smear which was made by Dr. W. B. Stone, pathologist of the Schenectady Laboratory Association:

"Not knowing the other features of the blood examination, I can only give the features of the stained smear. There is a very great variation in size of the various red corpuscles, and also a marked degree of poikilocytosis. There is a slight degree of polychromatophilia and I found one normoblast. The large cells are more numerous than the smaller ones. This is evidently a grave anemia and quite suggestive of the pernicious type, which is very rare in children; some do not admit its existence. Syphilis and rickets and other conditions, however, sometimes produce a blood picture similar to this."

The urine is negative as to albumin and sugar and contains no bile.

The mongolian effect is added to by a decided yellow tinge of the skin undoubtedly due to the anemia.

Most interesting is the fact that the twin brother, apparently well developed and many inches taller, gives a negative Wassermann.

Although no Wassermann has recently been made on the blood of the first child, who also shows the mongolian features, I understand that a positive reaction was obtained within the past twelve months.

This first child possibly conforms more nearly to the mongol type in that the head is somewhat flattened from behind forward and the circumference is possibly less than normal.

The nasal bridge is broad and the eyes slant slightly. The hands are stubby. She is 9 years old and has reached but the second grade in school, evidently of slow development mentally.

Her liver is markedly enlarged and the lower margin of her spleen disappears under the crest of the ilium.

The importance of syphilis as a direct causal factor in the production of mongolian idiocy has been suggested. There is, however, no evidence of more than an indirect relation, as suggested by Still,¹ through rendering the reproductive organs imperfect. Thomson² says there is no reason to think that congenital syphilis or alcohol has anything to do with the symptom.

The main interest in these cases lies in the following facts:

1. Syphilis has shown itself congenitally in one of twins and has left the other apparently uninfected.

2. They emphasize the likelihood of mistaking syphilis for mongolism.

The similarity of the symptoms of the two conditions has probably been responsible for the belief that syphilis may directly cause the defect.

The accompanying photograph shows well the difference in development of the twins and the mongoloid features of the smaller.

111 Union Street.

2. Thomson, John: *Clinical Examination and Treatment of Sick Children*, Edinburgh, 1908.

CLINICAL DEPARTMENT

TRAUMATIC RUPTURE OF THE LEFT KIDNEY *

CHARLES J. BLOOM, B.Sc., M.D.

AND

RUSSELL E. STONE, M.D., F.A.C.S.

NEW ORLEANS

INTRODUCTORY

The case we are to report is of interest both to the clinician and to the surgeon. Our main reasons for presenting same are twofold: first, on account of the rarity of these cases, and, second, because there were no objective manifestations of trauma.

Kuster, in 7,741 injuries at the clinics of Baser and Berlin, tabulates only 10 cases of injuries to the kidney, or a little more than 1:1,000. Of these 10 only one was similar to the case now to be presented. Of 2,610 autopsies under his supervision, there was only one of a penetrating nature. Israel reports only one operative case, notwithstanding his large experience in renal surgery.

REPORT OF CASE

Family History.—Irene C., aged 11 years, was the fifth child of six living children. Her father and mother give a negative history in every detail, and her family history with reference to tuberculosis, malignancy and insanity was negative.

Previous History.—Born at 9 months, normal delivery. Breast fed entirely for one year, and with soft food until she had reached the age of 32 months. From that time on she had received full diet. Prior to her present illness she had never needed the attention of a physician.

Present Illness.—In the forenoon, Aug. 5, 1915, while the patient was standing on the edge of a wagon, with one foot balanced on a swinging gate, her little brother pulled the gate in the opposite direction, causing her to fall. In falling it is evident that she traumatized the middle and left lower quadrants of her body. Following this, she fell from the wagon to the ground, a distance of about 3½ feet. She was unconscious for a few minutes, and after regaining her senses, complained of a "pain in her stomach" and about fifteen minutes later vomited. At 8 p. m., on the same date, she voided "a black urine," and at 9 p. m. had about 1 degree elevation of temperature. During the night she voided three times, the urine becoming clearer as time progressed. The following morning, Aug. 6, 1915, she had "frequent desire to urinate," however, unaccompanied by pain. She complained of a "drawing down pain" radiating from the region of the stomach to the vicinity of the kidney. She was admitted to Hotel Dieu at 9:15 p. m., August 6, her father having brought her there from Kenner, La.

* Submitted for publication October, 1915.

Physical Examination.—Well nourished, and fairly well developed. A careful inspection of the abdomen made by Dr. Stone and myself revealed some degree of tympanites, and a slight sensitiveness to touch. Other than her temperature being 102, pulse 136, respiration 34, there were no external manifestations of traumatism.

Laboratory Reports.—Total white count, 13,500; 77 neutrophils, and 33 small mononuclears. August 7 the urine had a specific gravity of 1.024, was acid in reaction and contained no albumin or sugar. A few hyaline casts were present, also a few red blood pus and epithelial cells, and cylindroids. August 10 the urine report was: Specific gravity 1.010, acid reaction, no albumin, or sugar; many red blood cells, and few pus cells; no casts or crystalline deposits.

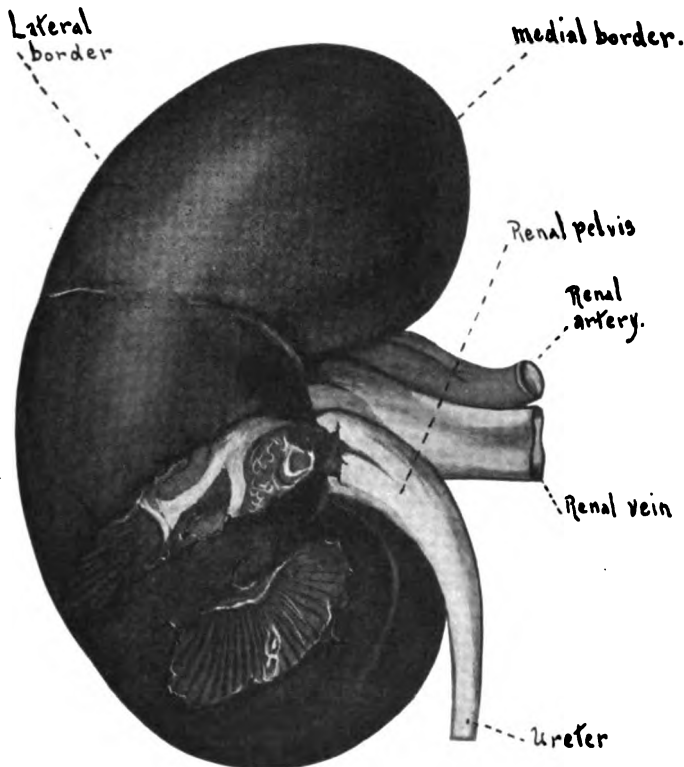
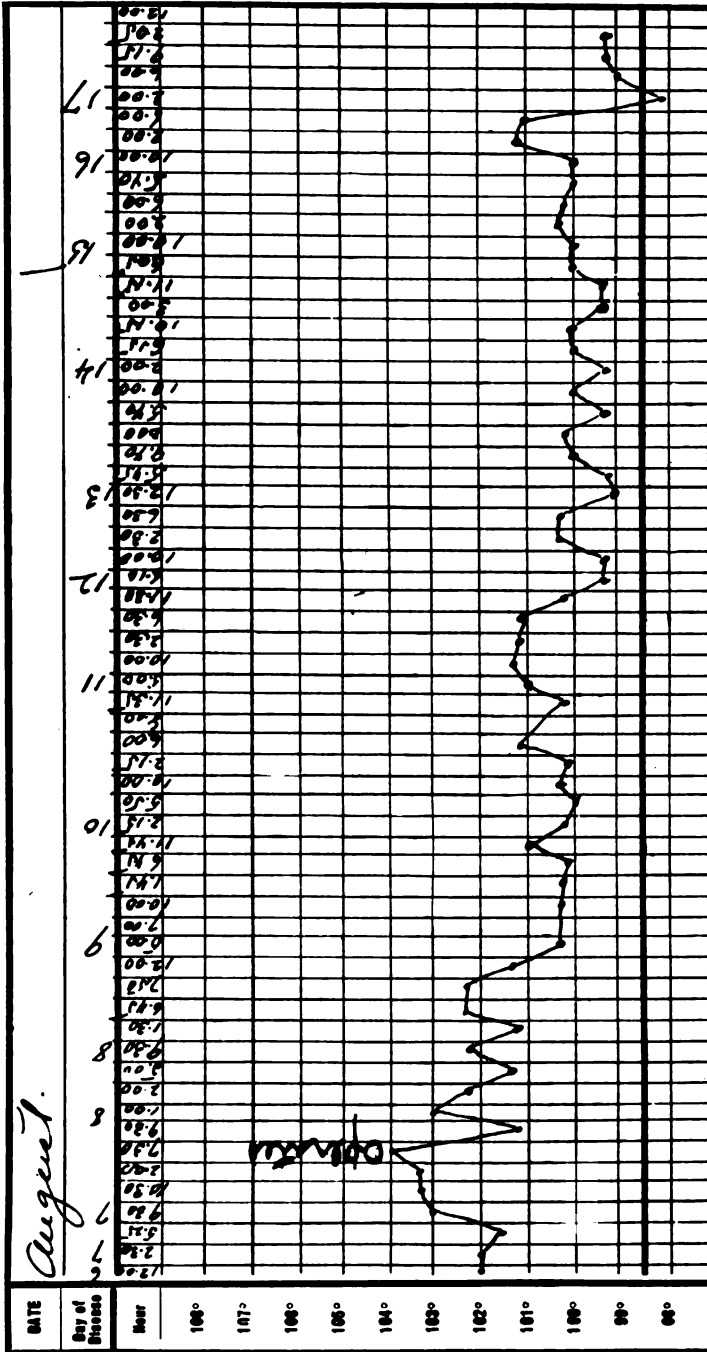


Fig. 1.—Drawing of ruptured kidney.

She was kept under observation twenty-four hours, but with an increased temperature, a weakened pulse, a certain amount of shock, a leukocytosis, with an increased amount of tympanites, and abdominal sensitiveness, a diagnosis of rupture of the left kidney was made, and we came to the conclusion that surgical interference was necessary.

Operation.—The operation was done under ether anesthesia, administered by Dr. Caine. The incision was made completely from the twelfth rib to the crest of the ilium. A large hematoma, firmly organized, was found, and this was removed with some trouble. On examination of the kidney we found two separate lacerations: one at the lower pole, the other about 3 inches above. The capsule was completely torn away, and in shreds; hence it was quite



impossible to suture the kidney. The field was irrigated with a saline solution, and a large cigarette drain introduced and the wound closed. The operation consumed thirty minutes, and as the pulse was 188 at the beginning of the operation, and 200 at the end, it was necessary to infuse the patient with 600 c.c. saline solution. The patient reacted nicely and improved daily until her discharge from the hospital on the ninth day. Drainage was removed on the fifth day, and urine from the wound discontinued on the seventh day.

Considering traumatic injuries of the kidney, the symptoms present in the majority of cases are, first, pronounced shock; second, pain in the lumbar region, particularly in the costovertebral angle, often radiating along the ureter to the region of the bladder, and hematuria of varying degree. In this case, although there was an external hemorrhage, the tumor mass which is sometimes seen, was absent. According to Tuffier, the injury in this case was one of the third degree: one in which the capsule was ruptured; in which there was an extra renal hemorrhage, with two deep, multiple, stellate fissures of the kidney substance, most pronounced below the hilum.

PROGRESS IN PEDIATRICS

RECENT ADVANCES IN ANATOMY, PHYSIOLOGY, AND PATHOLOGY OF CHILDHOOD *

JAMES B. HOLMES, M.D.

BALTIMORE

N. Pende¹ has described what he believes to be a new endocrinal gland. The structure has been found by him in puppies and in infants under 1 year of age. It occurs in the form of fifteen to twenty solid "epithelial islets," scattered around the parathyroids, thyroid and upper pole of the thymus, occasionally, also, at the lower pole, and more especially in the connective tissue of the superior outlet of the thorax.

These structures were found in making serial sections of the neck organs from the tongue downward. The author thinks it is not improbable that the glands have also a wider distribution.

In newlyborn infants the largest masses may be seen, at times, as grayish red points that through their richness in vascular capillaries stand out against the suprathymic or periparathyroid connective tissue.

The conformation of the islets is said to be microscopically quite characteristic. They consist of a mass of closely packed cells pierced by a rich capillary plexus, and almost always lacking any firm connective tissue stroma.

The masses have no capsule but are separated from the adjacent structures by loose connective tissue in such manner that the individual groups of cells appear, microscopically, as true, sharply defined, islands.

The individual cells are large, having two or three times the circumference of the parathyroid cells in the same individual. They are described as having the appearance of epithelial cells, being round or polygonal in form, with very definite margins to the protoplasm, and having a very large, centrally placed, round epithelioid nucleus, with a delicate nuclear membrane, a scanty chromatin network and several nucleoli. In many cells the nucleus is smaller, homogeneous, and

* Submitted for publication Nov. 7, 1915.

1. Pende, N.: Ueber eine neue Druse mit innerer Sekretion (*Glandula insularis cervicalis*), *Arch. f. mikroskop. Anat.*, 1914, lxxxvi, No. 1, p. 193; also *Riforma med.*, 1913, No. 22.

deeply-staining. The cytoplasm consists of numerous small granules so thickly placed that the protoplasm often appears to be stained homogeneously.

In a small number of cells there are seen scattered, larger, drop-like granules which stain well with eosin and other acid stains, but poorly with basic stains. In many cells the protoplasm has a vacuolated appearance. Such cells are met infrequently in the newly born, but their number increases rapidly with increasing age, and especially, says the author, under pathologic conditions. By the end of the first year there is visible a more or less large mass of vacuoles in practically all the cells. These vacuolated cells show then a small pyknotic, eccentrically-placed nucleus of variable size. The after fate of these cells, and the evolution of the islands generally, has not yet been studied; further investigation is in progress.

By applying Ciaccio's method of staining for lipoids, Pende has found that most of the granules are lipoidal in nature. As vacuolization proceeds, true fat globules appear in the place of these lipid granules with increasing frequency. No pigment granules or other metaplastic structures such as glycogen granules are seen. The chromaffin reaction is negative.

No glandular lumina, cysts, follicles, or enclosed colloidal spaces are present. For this reason Pende thinks that the bodies are not remains of the so-called *post-branchial bodies* on the one hand, nor rudimentary portions of the adjacent glands of epithelial origin, the thyroid, parathyroid and thymus, on the other. The structure of the islands is quite different from that of the last mentioned glands.

The author's statement that these new glands of internal secretion remind one in detail of the appearance of the suprarenal glands, is noteworthy. There are many points about the above description of the new gland that may be applied to the appearance of embryonic fat, and masses of this, it will be recalled, are often met about the poles of the kidneys in the newly born, and in their resemblance to the suprarenal glands, have not infrequently caused confusion.

Prof. Pende is First Assistant in the Institute of Medical Pathology at Palermo. The result of his further studies, which are now in progress, will be awaited with much interest. Excellent plates accompany the present report. A brief, earlier report was made in the *Riforma medica*, 1913, No. 22.

During the past year two studies have been made bearing on the nutrition of infants. Benestad² has subjected the problem of initial loss of weight in the newly born to further analysis. Carlson and his

2. Benestad, G.: Wo liegt die Ursache zur physiologischen Gewichtsabnahme neugeborener Kinder? *Jahrb. f. Kinderh.*, 1914, lxxx, No. 1, p. 21.

collaborators have utilized the reappearance of gastric contraction-waves in the infant to determine the proper interval of feeding.

The initial loss of weight in the newly born has long been known. Scientific attention was directed to it about a century ago by Chaussier, and the fact now finds appropriate statement in all textbooks of pediatrics. The loss begins promptly after separation of the child from the mother and continues until, on the average, one fifteenth to one seventeenth of the original body weight is lost. The recovery from the loss begins usually about the third or fourth day after birth. During the next week the infant recovers its original weight, i. e., by the end of the tenth day.

This phenomenon is not peculiar to the human species. It occurs in some other animals, e. g., guinea-pigs (Edlefsen). It does not occur, or is a very infrequent phenomenon in dogs, cats and rabbits (Kehrer).

As shown by L. Faye, in 1874, the loss consists largely in water, by means of the insensible perspiration, the respiratory loss, the very considerable water content of the meconium, and the scanty urine.

During the first two or three days Nature does little to supply this loss. The child receives only a small amount of colostrum (100 c.c.) to oppose a relatively large loss of fluid.

Some years ago it was reported that this initial loss could be prevented by supplying the child with food during the interval elapsing before the maternal supply appeared, and recently Bailey and Murlin³ have recommended feeding newly born infants, in addition to the breast secretion, a formula of about the same composition as colostrum.

If this initial loss of weight is a normal and inevitable phenomenon it must be accepted as such. Clearly the meconium is an accumulation formed in the intestines during the course of development. It may be regarded as waste material, and no more a true part of the newly born infant than the vernix caseosa. If so, the average weight of this substance might properly be deducted from the average birth weight—about 200 gm.—which, together with the urine voided, would be about one-half the total loss. The older texts taught that the colostrum was laxative in its action on the infant and was Nature's provision for freeing the organism of the meconium. It is not inconceivable that some other part of the initial loss of water may represent a necessary riddance. If the initial loss is necessary or inevitable the pediatricist must be tolerant of it and he may solace himself with the thought that the true loss of weight is not really so great as it seems.

3. Bailey and Murlin: *Proc. Soc. Exper. Biol. and Med.*, 1914, xi, 109.

If, however, the phenomena of the early days of lactation, the production of colostrum and the delayed appearance of milk constitute another imperfect adaptation on the part of Nature, then clearly the attending pediatricist may hope to render the adaptation more perfect. He may supplement the existing provision for supplying fluid to replace that which is being lost. He may feed the child in the interval that elapses before the natural supply of food becomes available.

Benestad has reviewed these points. He finds that the extent of the loss of weight depends, (1) on the degree of development of the infant, (2) on the actual weight at birth, and (3) on the milk supply of the mother. Another factor that is less frequently operative seems to be great loss of blood in the mother (presumably through subsequently diminished milk flow). The severity of the birth process does not in itself appear to be a factor.

The studies of numerous workers (Winkel, Gregor, etc.) have shown that premature infants lose proportionately more weight than full-term infants. This is true even when the latter are small infants at birth (3,000 gm.). The percentage of the birth weight lost decreases with the maturity of the infant. This, the author thinks, is due to the greater deficiency of the digestive apparatus in the mature child.

Newer studies have shown that the more important enzymes are present in the digestive tract of viable premature infants. Formerly it was believed that many enzymes were not present until some weeks after birth. Langstein and Soldin have found erepsin as early as the thirtieth week. The demonstration of the mere presence of these enzymes does not prove, however, that they are present in quantities sufficient for the digestion of the volume of food received by a young infant from its mother.

The failure of all efforts to prevent the initial loss of weight, says Benestad, or even appreciably to diminish it, by supplying newly-born infants with milk from wetnurses, whose children are but a few days older than the patient, seems to indicate a functional inability to utilize the milk during the first days of life, even in a mature infant. Forcing food at this time may even delay the normal recovery of the birth weight (Altherr).

An initial loss of weight is not present, or is very transitory, in most mammals that have been studied. The period of infancy also is shorter in all other animals than the human species. It would be but in accord with this if it were found that the digestive functions were more complete at birth in young animals than they are in the human young. Bahrdt and Langstein's studies show that the calf possesses the power to reduce albumin to amino-acids, even in the first days of

life. Simon's studies led him to the conclusion that in the human infant the breaking down of the albumin molecules stopped at the polypeptid stage, instead of proceeding to the amino-acids and ammonia. These polypeptids formed 10 per cent. of the total nitrogen output in the urine of the first few days, or double the percentage found in the adult. The percentage gradually diminishes and reaches normal by the end of the first week, the proportion of amino-acids and ammonia rising. It would seem that the human infant in contrast with the young of other mammals (for example the calf) is unprepared during the first days of life completely to digest albumin. Similar comparative studies have not been carried out on premature infants. They are, presumably, still less prepared to digest albumin. During intra-uterine life the organism is supplied by the products of maternal digestion—serumalbumin, sugar, and human fat. A shorter or longer period is required for adjustment to the conditions of extra-uterine life in which the organism must itself break down the higher compounds and elaborate them anew. Some days are, as a rule, necessary; the period is longer, or the process less rapid, in the case of premature infants. This period of defective digestion may be accompanied by a period of defective assimilation; the two can scarcely be separated.

Where infants are of the same degree of maturity the average initial loss varies with the birth weight. Infants weighing 3,000 gm. lose, on the average, 175 ounces (5.36 per cent.) during the first three days, while those weighing 4,000 gm. lose, on the average, 252 gm. (5.91 per cent.). As is seen, the difference in percentage loss is not great. It has not been shown on what this small difference depends.

Finally, the initial loss of weight depends on the milk supply of the mother. The most suitable food for the young infant is colostrum. Its fat and its serumalbumin are closely related to those to which the infant has been accustomed in its intra-uterine life, and if not fully broken down in the immature digestive processes are perhaps less liable to prove toxic. No other food can wholly replace it. With improvement in the digestive processes an increasing supply of mother's milk becomes necessary. In the meantime, says the author, artificial feeding increases and prolongs the initial loss of weight.

Williamson⁴ has recently repeated and extended the early work of Leichtenstern (1878) on the hemoglobin content of the blood of the newly born. He examined over 900 patients ranging in age from 1 day to 76 years, and over. He employed the spectrophotometric method and the principle of extinction coefficient as developed by

4. Williamson, C. S.: Influence of Age and Sex on Hemoglobin. A Spectrophotometric Analysis of Nine Hundred and Nineteen Cases (Preliminary Report), *Jour. Am. Med. Assn.*, 1915, lxxv, 302.

Vierordt and Hüfner. Details regarding the method and the author's application of it may be found in the original publication. Only that part of the work that relates to infants and young children will be discussed here.

The infants and children examined were as follows:

TABLE SHOWING NUMBER OF CHILDREN EXAMINED AND THEIR AGES

Age	Number of Cases		
	Male	Female	Total
1 day	16	15	31
2- 3 days	15	16	31
4- 8 days	15	18	33
9-13 days	15	15	30
2 weeks-2 months	15	15	30
3- 5 months	16	16	32
6-11 months	18	15	33
1 year	18	16	34
2 years.....	16	17	33
3 years.....	15	16	31
4 years.....	16	15	31
5 years.....	17	18	35
6-10 years.....	18	15	33
11-15 years.....	17	20	37

The material for the study was selected with care, effort being made to include only strictly normal, healthy individuals. The great majority of the babies were breast fed and all were thriving and gaining weight in a normal manner. A considerable proportion of the older children were school children and were studied early in the fall just after the closing of the summer vacation, and when their physical condition was presumably at its best.

The course of the hemoglobin percentage may be seen in the accompanying Chart 1.

After birth the percentage of hemoglobin begins to diminish at once, and after two weeks the decline is very rapid. By the fifth month the average value is very nearly down to the minimum (about 10/17 the value at birth) and far below the average value at 16 to 20 years (adult value). There is seen a very slight further decline at about 1 year, and thereafter a steady increase until the normal value is reached at 15 to 16 years. Thereafter there are but slight variations, with, toward old age, a slow decline.

The rapid decline in the amount of hemoglobin during the first five months is a highly characteristic feature of the age curve, says the author.

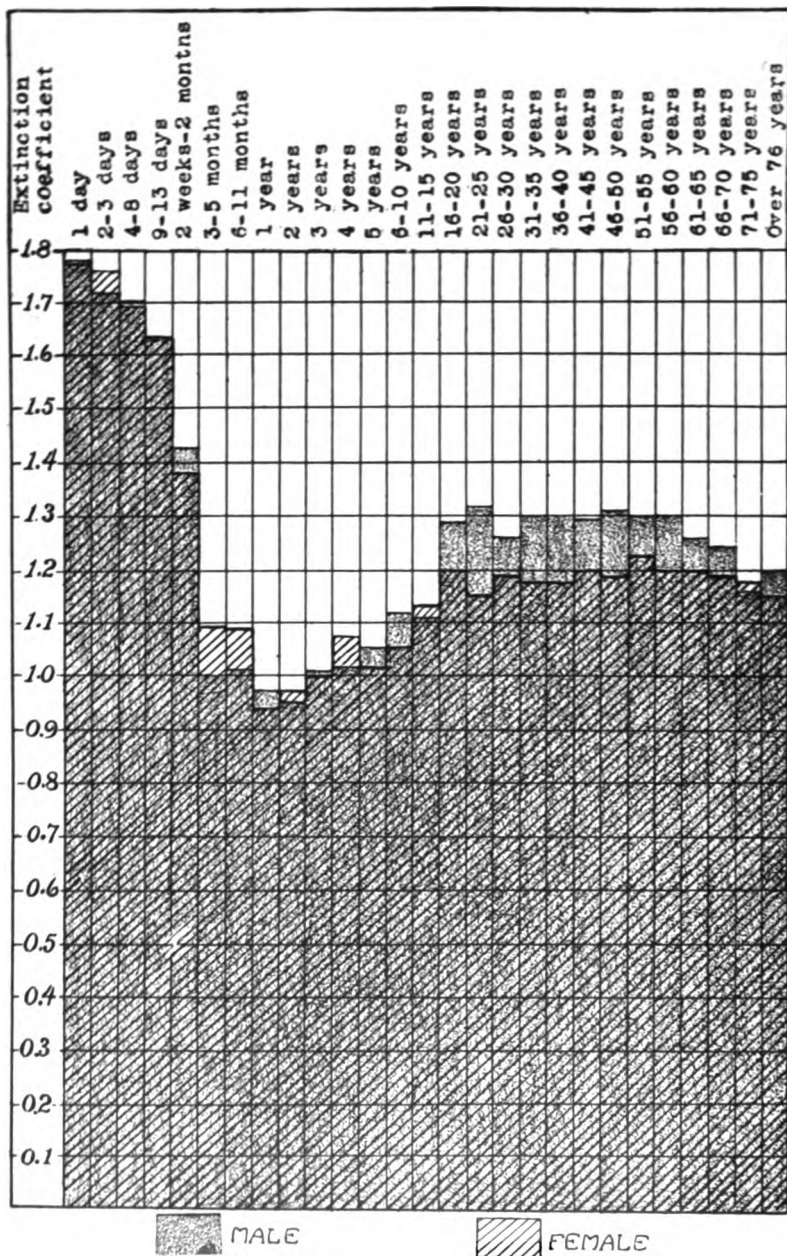


Chart 1.—Curve showing influence of age and sex on hemoglobin percentage. Shaded areas indicate males; diagonal lines, females.

In selecting the material an effort was made to have the two sexes equally represented in each age period. A comparison of the hemoglobin values obtained shows that up to the fifteenth year the hemoglobin content of the blood is almost precisely the same for the two sexes. After the fifteenth year sex differences make themselves plainly evident; the values for the women are, in every instance, considerably lower than those for the men; with age the difference grows less.

The practical conclusions that may be drawn from Williamson's work are:

1. Instruments which are graduated in percentages of a supposed average normal individual can not be utilized for making determinations in children of different ages without correction.

2. During the first two weeks the normal hemoglobin content of the infant is about 36 per cent. greater than that of the normal adult. Between the second and third months it just equals that of the normal adult and from the fourth month to the fourth year it is normally only about 80 per cent. of that of the adult (slightly less during the second and the third year.) The percentage rises gradually thereafter. No correction for sex is necessary.

3. Pediatricists should accustom themselves to allowing for the natural variations in hemoglobin at different ages.

The author gives the following example to illustrate the errors that may arise from disregarding these facts:

Let us say that a mother who is 22 and a father who is 24, and two children, a boy of 1 year and a girl of 2 years, respectively, all being averaged as normal individuals, have their blood examined with any of the instruments which are graduated on the basis of an average normal adult. An inspection of the table with reduction to percentages, will make it evident that the values will be, father 100 per cent., mother 87 per cent., boy 1 year, 74 per cent., girl 2 years, 74 per cent. It thus appears that the mother is anemic to the extent of 13 per cent., and that both children are markedly anemic, to the extent of 26 per cent. The fact is that the mother and both children have the amounts of hemoglobin which they should have for the respective ages and sex. The anemia is merely apparent, and due to the fact that the hemoglobinometer was not calibrated to read in absolute terms, and that the physician did not take the age and sex variations into consideration.

Several papers upon congenital icterus have appeared during the current year. The most extensive and significant paper upon the subject is that from Arvo Ylppö⁵ of Langstein's clinic. Ylppö reviewed the various theories of congenital icterus and our knowledge of the occurrence of biliary pigments in the blood, stools and urine, and restated certain methods that have been employed in the past in

5. Ylppö, A.: Icterus neonatorum (incl. I. n. gravis) und Gallenfarbstoffsekretion beim Foetus und Neugeborenen, *Ztschr. f. Kinderh., Orig.*, 1913, xi.

attempts to determine their presence quantitatively. He introduced the spectrophotometric method of determining the presence of biliary pigments quantitatively, and described the technic that he found applicable in the case of blood, urine and stools. He pointed out certain limitations of the method, but retained it as the most accurate method yet found. With it he investigated the secretion of biliary pigments in the fetus and the newborn, and the relation of the secretion to icterus neonatorum and icterus neonatorum gravis. He first took up the excretion of biliary pigments in the stools and urine.

His material consisted of 6 full-term infants that showed various degrees of icterus, 2 full-term infants that were not icteric, and 2 premature infants. All were examined throughout the first thirteen days of life and two full-term infants were examined between the eighth and twelfth week. One of the premature infants was reexamined in the sixth week.

The infants were placed in metabolism beds directly after delayed tying of the cord, and were kept there for thirteen days, being removed only for nursing. The meconium, the stools and the urine were collected separately and examined. A distinction between meconium and breast stool was made with the eye, or where this proved difficult, was established by the presence or absence, microscopically, of lanugo hairs. The infants were rated in four grades according to the amount of icterus present.

It was found that the weight of the meconium (dried, and in some instances freed from fat) obtained, varied from 0 to 23.23 gm., depending on the amount lost at birth, and that the biliary pigment contained in it averaged 22.5 mg. (0 to 63.43 mg.). The amount of biliary pigment obtained did not vary closely with the amount of meconium recovered.

In a later portion of his report the author established to his satisfaction that the placenta is an effective barrier against the passage of biliary pigments from the blood of the fetus to that of the mother. The amount of biliary pigments excreted during intra-uterine life may thus be estimated from the amount found in the meconium. This total Ylppö placed at about 33 mg.

He drew the following conclusion from his study of the excretion of bile pigments, stools and urine:

Up to the last month of intra-uterine life the formation of bile pigments is minimum. During the last month a striking increase may be demonstrated. During the whole fetal period there is in any case only about 33 mg. of biliary pigment excreted.

The increase in the formation of bile pigment which is recognizable in the last month of fetal life is definitely accelerated with the begin-

ning of extra-uterine life. From about the sixth day of life on, an especially rapid increase in the formation of bile pigment can be seen.

In the first thirteen days a total of about 140 mg. of bile pigment is excreted; of this, 0.5 to 1.6 per cent. (according to the intensity of the icterus) is excreted in the urine of icteric infants, and only minimal amounts, at most 0.1 per cent., is excreted in the urine of nonicteric infants. The total amount excreted shows no noteworthy difference between the icteric and the nonicteric children, and there is not a larger amount excreted in corresponding intervals in icteric infants.

There is no correspondence between the intensity of the icterus and the total amount of bile pigment that is excreted.

With these findings, the foundation, he says, falls from under all those haenatohepatogenous theories which refer icterus neonatorum to an absolutely large destruction of red blood cells in the icteric infant.

Ylppö then turned to the examination of the biliary pigment content of the blood. The circulating blood of normal adults contains a minute amount of bilirubin as Gilbert and Heracher have shown. Hammersten had shown that this is true also for the horse. Gilbert, Lereboullet and Stevens found that the amount is increased in the blood from the umbilical cord and from newly-born infants, as did Biffi and Galli.

Ylppö examined sixty-one children in this regard, including eighteen premature infants and two fetuses. The blood of some of these was examined from five to eight times, just after tying the umbilical cord and then at intervals during the course of the next few weeks. In some instances that of the mother was examined before, during and after childbirth. The findings are summarized thus:

The content of the fetal blood in biliary pigment is increased in comparison with that of healthy adults.

At the time of birth there is found a still more marked increase, which cannot be brought into relation with the conditions of birth (length, severity, etc.).

Those infants which have an especially high content of biliary pigments in the blood of the umbilical cord all become jaundiced, while those which have a strikingly small amount of pigment in the blood do not, as a rule, have jaundice.

After birth the content of biliary pigment in the blood rises in each child. This increase lasts three or ten days and varies in the rapidity with which it increases.

Children in whom the biliary pigment content of the blood exceeds a certain definite (but not sharply defined) *level for cutaneous jaundice*, become jaundiced.

The intensity of the cutaneous icterus shows a correspondence with the content of the blood in biliary pigment.

Infants in whom the amount of bile pigment in the blood ceases to increase by about the third day, and in whom the total content remains under the level for cutaneous icterus, do not become jaundiced.

Premature infants generally show the very high content of biliary pigment in their blood. This continues to increase ordinarily for six to ten days in them, and the amount of pigment in the blood remains above the level for cutaneous icterus for a week or more.

The result of Ylppö's clinical studies are summarized in the following sentences:

All viable premature infants (under 2,500 gm.) show icterus neonatorum: A great majority of them show a very intense icterus that lasts several weeks (forty-two of them were studied).

Eighty-two per cent. of the 355 full-term infants examined showed jaundice. They differed clinically from infants that did not show jaundice, only in so far as those in whom the jaundice was very outspoken, showed secondary symptoms, characteristic of cholemia (drowsiness, itching, etc.).

Three distinct forms of icterus neonatorum were distinguished: Icterus neonatorum simplex; icterus neonatorum prolongatus (duration over two weeks); icterus neonatorum gravis. Their unity was shown through the presence of all possible transitional forms and they are therefore to be looked on as being only various types of a single disease, icterus neonatorum.

This disease, icterus neonatorum, shows great independence in its course and is not influenced by secondary infections or trauma.

Data is then given to support the theory that there is in puppies an increase in the amount of circulating biliary pigments similar to that which appears in the human infant, but that it takes place in utero, and has almost or quite passed away at the time of birth. In the puppy the excess of pigment is laid down in granules in the placenta. In the human infant the phenomenon appears nearer the time of birth. A few granules of pigment may be deposited in the placenta (never any appreciable amount); the bulk of the pigment circulates in the blood until it is withdrawn by the liver or passes out in the urine (a small portion at most), and if present in more than a certain fixed percentage causes cutaneous icterus.

Only the horse and man show bilirubin in the blood normally, and only the young of these two mammals show icterus neonatorum.

The injection of bile pigment into the blood-stream of animals shows that in newly-born puppies and in adult dogs the liver quickly

removes the circulating pigment and passes it out as bile, minimum amounts only (much larger in the newly born) passing off in the urine. Administration of bile pigments by mouth yields no evidence, we are told, of the absorption of unreduced bile pigment from the intestine. Only man and the horse, says Ylppö, show bilirubin in their blood under normal conditions, and in these two animals only can it accumulate in the blood in the absence of injury to the functions of the liver.

As has been seen, Ylppö does not believe that infection plays any important rôle in the etiology of congenital icterus. When he began his work he thought infection played an important part. For this reason, he was especially watchful for any evidence pointing to a relation between infection and icterus in the cases studied by him. He found, on the contrary, that icterus neonatorum ran its course quite independently of infections, whether enteral or parenteral. (The infections whose influence was observed by him were aspiration pneumonia, tetanus neonatorum, umbilical sepsis, intestinal infection, and syphilis.) The fact that icterus neonatorum begins while the child is yet in utero would in itself weaken any theory of an infectious origin for it.

The fact that the percentage of circulating biliary pigment has already begun to increase before the time of birth, shows that the change is not dependent alone on postnatal circulatory changes, if it is dependent on them at all.

In the fact that the incompletely broken down albumin radicals are allowed to pass from the portal system of the newly born, through the liver, into the general circulation whence they are excreted in the urine, Ylppö sees further proof of functional immaturity of the liver in the human fetus at birth. As regards the maturity of their livers, the human young, he says, like the young of the horse, are born prematurely. And premature infants are, as regards the liver, doubly immature.

The mature liver when normally functioning secretes the bile into the bile capillaries. The fetal liver secretes its bile into the blood stream where it enters a closed circuit, very little of it being excreted in the urine in utero and little (in man) being laid down in the placenta. The excess is laid down in the liver itself. There is little excess, for little is produced.

Near the time of birth the liver normally begins to excrete bile into the bile capillaries. The more mature the liver is at the time of the birth of the infant, the more completely will it do this and the more perfectly will it keep the content of the blood in biliary pigments below the level at which icterus is produced. The less mature it is the less effectively will it do this and icterus neonatorum will appear in pro-

gressively severer grades. In the premature infant the liver is so immature that jaundice always results. In any case the depth of the jaundice (i. e., the content of the blood in biliary pigments) and the persistence of the jaundice are indicative of the length of time that passes after birth before the liver comes to the normal or necessary degree of functional maturity.

Such is Ylppö's theory of the etiology of congenital icterus. He portrays it schematically in the accompanying diagram (Fig. 2).

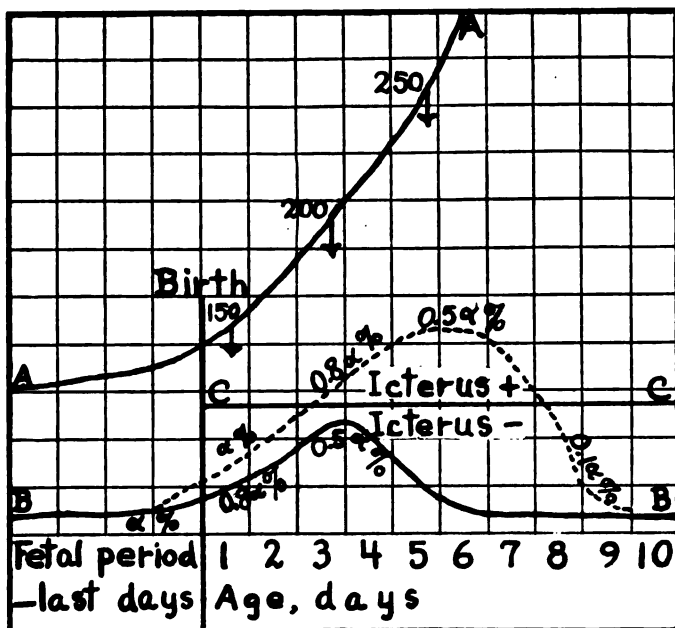


Chart 2.—Diagram of secretion of biliary pigment in icteric and nonicteric infants. Line A-A, pigment formed=100 per unit of time; line B-B, percentage in nonicteric infant; C-C, level for icterus of the skin; dash line, percentage of pigment passing into the blood in icteric infant; solid line percentage in nonicteric infant.

In this diagram it is shown that there is a slow increase in the production of bile pigments per unit of time during the last days of intra-uterine life, and that this rate increases rapidly and continuously after birth. The older the child is, the more bile does the liver secrete, as is shown by the author's analyses. There is no rapid production of biliary pigment at or shortly after birth followed by a subsequent decline in production, as has often been assumed. It is inferred that any change noted in the count of the red cells of the blood or in the hemoglobin content of the blood at or near the time of birth is merely a concomitant phenomenon.

A. Hirsch,⁶ of von Pirquet's clinic, reported a less extensive study of icterus neonatorum. She employed less accurate methods than Ylppö, but reached similar conclusions.

A more recent publication is that by Fridtzof Bang⁷ of Copenhagen. Bang used the Gmelin-Gilbert-Sunde method of estimating bile pigments in the blood and reached results that are substantially in accord with those of Ylppö. His publication is chiefly of interest in its criticism of Ylppö's deductions.

Bang holds that Ylppö has not demonstrated in a conclusive manner that bile pigment discharged into the intestine may not be reabsorbed in part, and, passing around the liver through the *ductus venosus Arantii*, get into the general circulation.

Ylppö denied that there is any *sudden* increase in the percentage of bile pigment in the blood at or immediately after birth. Bang believes that there is such, and offers diagrams to prove it. He finds in this phenomenon proof that some new factor enters into the production of bile pigment at the time of birth. He theorizes as to what it may be.

Ylppö had attributed the accumulation of bile pigment in the blood of the newly born to a defective functioning of the immature liver parenchyma and held this was more marked in premature infants. Bang assumes that the fetal heart and the circulatory mechanism are at fault, and sees the cause of the abnormal biliary secretion in venous stasis.

At birth the pulmonary circulation is suddenly augmented, the placental circulation is interrupted. The heart of the newly-born infant is unable to adapt itself at once to the changed conditions. It needs time to make the adjustment. The regulating mechanism, cutaneous and other, is still imperfect, and stasis results in the liver and elsewhere.

As a result of stasis in the cutaneous capillaries, serum escapes into the tissues and the blood becomes concentrated, the hemoglobin index rises and also the count of red cells. As a result of stasis in the liver, the concentration of bile-pigment in the blood rises. It does this to a slight degree during stasis in adults (figures are given) and in infants the phenomenon should be more marked because the weight of the liver is relatively much greater with respect to the blood volume—56 to 77 instead of 28 to 77. As the heart gradually adapts itself to the changed conditions of circulation, the stasis passes away, and with it

6. Hirsch, A.: Die physiologische Icterusbereitschaft der Neugeborenen, Ztschr. f. Kinderh., Orig., 1913, xv.

7. Bang, F.: Recherches sur l'origine de l'ictère des nouveau-nés, Arch. mens. d'Obst. et de Gynéc., 1915, viii, 296.

the jaundice. The weaker heart of the premature infant requires longer to adapt itself, hence the jaundice persists longer.

The whole discussion is highly theoretical.

How often the healthy baby shall be fed and how much shall be given him at a feeding, are fundamental questions in pediatrics, yet there is no unanimity regarding this. Examination of recent textbooks and pediatric writings makes this clear. Great variety of opinion is expressed by leading teachers. The intervals advocated range from two hours for the first month to three, three and a half, and even four hours. Taken as a whole, American writers seem to prefer short intervals, while continental writers incline toward longer intervals. Some advocate shorter intervals in breast feeding, and longer ones in artificial feeding.

The normal healthy human infant, as the young of all animals, nurses when the sensation of hunger becomes strong enough to be uncomfortable, provided food is at hand at the time.⁸ When careful records of nursing babies have been kept, it has been found that not only do the intervals between apparent inclinations to nurse vary greatly, but also the amount of food taken at a nursing varies. In the same child the length of the intervals may vary from 1 hour to 6 hours; the amount of milk taken at a nursing from 1 to 3 ounces, or more widely. Even when the child is placed at the breast at regular intervals he may yet vary the amount of milk taken at each nursing. These variations depend on factors within the child, such as hunger, and on others beyond his control, e. g., the amount of milk in the breasts at the time of suckling, and the comfort of the child while nursing.

The apparently arbitrary regime selected by the pediatricist has been chosen because it works. It is in a great measure empirically chosen. It is the mode of feeding that the individual finds works best in the majority of infants that come under his care. It is generally agreed that the regular feeding at stated intervals is desirable. Opinions differ as to amount of food to be given at a feeding and as to the interval that is most desirable. The two are in a measure, reciprocals of each other.

The total daily amount of food necessary for a healthy infant of a given weight and age has been rather satisfactorily determined by the statistical methods of Camerer and the experimental methods of Heubner. One hundred and ten calories of food pro kilo body weight is needed during the first month. This gives the total amount of food for the day. If, now, a three hour interval is selected, eight feedings

8. Ginsberg, H., Tumpowsky, I., and Carlson, A. J.: The Onset of Hunger in Infants After Feeding. A Contribution to the Physiology of the Stomach, *Jour. Am. Med. Assn.*, 1915, lxiv, 1822.

in twenty-four hours, one-eighth of the total amount may be given at a time. If a four hour interval is selected, six feedings of one-sixth the total amount must be given.

The question at once arises, has the infant's stomach capacity enough to receive the large amounts of liquid that are necessitated by the feedings at long intervals? The answer to this question has been sought in two ways. First, the actual capacity of the infant's stomach has been determined post mortem; and second, attempts have been made during life to give these amounts of food. Studies of the actual capacity (after death) of the infant's stomach have been made by the various authors. The picture given by Holt in the fifth edition of his textbook of diseases of children, life-size illustrations, are readily available. They show that the stomach of an infant during the first month has a capacity of 1 to something over 2 ounces. That is, the capacity is not sufficient to receive the amount of breast milk required for each feeding at four hour intervals. Still less would it seem sufficient to receive the greater amount of fluid that is necessary for giving cow's milk in suitable dilution. Clinically, however, the infant's stomach is usually able during life to receive either amount, and that without unpleasant symptoms. The explanation lies in the fact that five, ten, or more minutes is consumed in taking the fluid, and that the liquid begins to leave the stomach within a few minutes after the first enters. The actual volume capacity of the stomach, post mortem or intra vitam, is thus not necessarily a true guide to the amount of fluid to be given at any one time. Nor is it, as a rule, a sufficient guide to the most desirable interval between feedings. It is certain that many infants do unusually well when nursed (or fed) at intervals of four hours from the first days on.

When the stomach has once been filled more or less completely, it seems desirable not to introduce more food until that previously given has completely passed out. Otherwise symptoms of indigestion are likely to result. It may even be that a somewhat longer delay is desirable. A certain period of rest for the gastric glands may be beneficial.

The roentgenogram studies of Pisek and LeWald⁹ seem to show that "three hours is practically the emptying time of the child's stomach, and often less than that." Czerny and others had earlier concluded that the stomach of the normal infant empties itself in from about one and a half to two hours. Whether the use of bismuth and other substances for Roentgen-ray work has any influence on the rate of emptying is perhaps debatable; many state that it has not. Normally, the time of emptying the stomach seems to depend on the quan-

9. Pisek and LeWald: *The Infant Stomach*, Tr. Am. Ped. Soc., 1913, xxv, 150.

tity of food taken, the rate of gastric secretion, and the vigor of gastric (digestion) peristalsis.

In any case satisfactory determination of the capacity of the stomach for receiving an amount of food, and of the time required for emptying the stomach after receiving the amounts given, is not all that is needed for the selection of the optimum amount of food and the optimum interval. It may be well to allow the stomach a period of rest between feedings. It may also be well to await the appearance of the sensation of hunger before introducing more food. Here again there is difficulty.

Until the last few years there has been no certain objective criterion for the existence of hunger. Such a criterion has now been found, it is thought.

In work published by Cannon and Washburn¹⁰ in 1912 and by Carlson¹¹ in 1913, it seems established that a "subjective sensation of hunger is caused by a certain type of contraction of the fundal end of empty stomach stimulating sensory nerves in the wall of the stomach." These contractions are peculiar to the cardiac and fundal ends of the empty stomach, and are, in normal individuals (adults) at least, "an objective index of hunger." Their presence is determined by introducing into the stomach a small balloon connected with a chloroform manometer. (For technic, see articles here referred to.)

Carlson⁸ and his collaborators have applied this method to determine the time of onset of hunger in infants after previous feeding. The determination of this question may aid in fixing the time that should elapse between the nursings of normal infants.

Their observations were made on thirty normal infants, from twenty-four hours to four weeks old. The frequency with which the infants were being fed and the amounts they received are not stated. They seem to have been breast-fed ("nursing") infants. The balloon was introduced into the stomach half an hour or more after feeding and the tracings published were obtained from infants who were asleep or otherwise quiet. Introduction of the balloon directly after nursing led to vomiting of the balloon and part of the food, and restlessness on the part of the child caused the inhibition of the hunger contractions.

Fifty-five observations were made upon the thirty infants. Tracings made from the chloroform manometer while the inflated balloon was in the fundus showed practically no contractions when the stomach was full. As the stomach gradually emptied itself feeble tonus contractions appeared. These increased in rate and intensity until, about two and a half hours after a nursing, they passed over into typical

10. Cannon, W. B., and Washburn, A. L.: *Am. Jour. Physiol.*, 1912, xxix, 441.

11. Carlson, A. J.: *Am. Jour. Physiol.*, 1913, xxxi, 175.

hunger contractions. In Carlson's series the minimum time elapsing before the appearance of hunger contractions was two hours and the maximum time was three hours. The time of onset of hunger contractions after the previous feeding varied for each infant. The hunger contractions of the empty stomach were seen to be modified tonus waves of the fundus of the digesting stomach.

The authors conclude: In the normal individual the presence of vigorous hunger contractions is probably biologic evidence that the stomach is in proper condition to receive fluid. If this is the case, the stomach of a normal infant is ready to receive food from two to three hours after the previous feeding.

From what has already been said, it is clear that, even if the reliability of the method used by Carlson and his associates be granted, many factors must be taken into consideration before pediatricists can accept the above evidence as indicative of the proper feeding interval.¹²

A paper by Smith and LeWald¹³ emphasizes the importance of placing infants in a semi-erect position during and immediately after nursing, and puts the instinctive inclination of mothers to lay colicky babies over their shoulders and fondle them, on a scientific basis. In the stomach of every individual there is a certain amount of gas. It may be derived from swallowed air, from gastric fermentation or from the intestines. In the large majority of cases, swallowed air accounts for the gas in the stomach. The size and anatomic relations of the pharynx are such that it is unable to close down completely on the small quantity of fluid swallowed at each gulp and, as a result, a certain amount of the air that is always present in the pharynx is carried down by the contraction of the muscles in the act of swallowing. When food is semisolid and a bolus is formed, less air proportionately is carried down.

Smith and LeWald introduced their study with a consideration of the anatomic position of the stomach. Roentgenography has shown that the stomach is not vertical in position in infants. The stomachs of infants resemble those of adults in a general way. The important features are these:

The esophagus enters the abdomen by an opening in the diaphragm, almost in the midline, in contact with the aorta and the ventral surface of the bodies of the vertebrae. The cardiac orifice lies just to the left of this position and the cardia is firmly held to the posterior abdominal wall by the esophagus as it pierces the diaphragm. The fundus of the stomach lies in the left para-vertebral groove, that is, in the lateral recess formed by the projection forward of the vertebral column into the abdominal cavity. The fundus reaches a plane considerably dorsal to the cardiac orifice. It is covered in front only

12. One cannot help wondering how far these waves were not simply evidence of increasing effort on the part of the empty stomach to expel the balloon, an indigestible foreign body.

13. Smith, C. H., and LeWald, L. T.: The Influence of Posture on Digestion in Infancy, *AM. JOUR. DIS. CHILD.*, 1915, ix, 261.

by the liver and extends to the anterior abdominal wall. The pyloric end of the stomach is pushed forward by the vertebral column, pancreas and duodenum. The pyloric opening is directed backward toward the duodenum, but lies in a plane which is ventral to that of the cardia. The cardiac opening is behind the center of the anteroposterior diameter of the stomach.

As food enters the stomach it gravitates to the lowest part, displacing any gas present to the highest part. If the infant is in a horizontal position the liquid food passes to the posterior portion of the stomach, that is, to the fundus, and any gas present is forced to the anterior part of the fundus and toward the right end of the stomach. They say:

Since the cardiac orifice is situated well back against the vertebral column it follows that it will be covered by the liquid and that the gas cannot escape into the esophagus. It can escape only through the pylorus, if at all. If the amount of food plus gas is enough to distend the stomach, either food or gas must be forced out through the pylorus or regurgitation of food must take place through the esophagus until the tension on the stomach wall is relieved. The horizontal position causes a perfect water-lock to form as far as the gas and the cardiac opening are concerned.

When the child is held upright the liquid gravitates at once to the dependent part of the stomach and displaces the gas to the highest part, that is, to the upper part of the fundus. This makes it possible for the gas to escape by the esophagus, and it often does so at once.

These conditions are well illustrated by roentgenograms. These were obtained from four infants ranging in age from 4 to 7 months, who were given their usual feedings of 4 to 7 ounces of modified milk, to which one-half ounce of bismuth subcarbonate had been added. They showed a progressive accumulation of gas in the stomach during the act of nursing. In two instances this was accompanied by regurgitation or vomiting. In one the accumulation of gas became relatively enormous; the distention of the stomach caused evident distress, and the infant refused to finish the bottle. Changing to an erect position, some minutes afterwards, caused a large eructation of gas, and the child at once stopped crying and went to sleep.

The presence of swallowed air is regarded by Smith and LeWald as objectionable. Extreme distention must be unfavorable to gastric secretion through pressure on the mucosa and blood vessels. The symptoms may often be entirely relieved by assisting the expulsion of the gas by mouth, so that it need not be passed through the intestine. If it does pass through the intestine, it causes colic. A horizontal position in nursing favors the accumulation of gas. Hospital feeding cases are often examples of the bad result of this. Except in the case of feeble infants, the feeding should be taken in five to ten minutes, or at most in fifteen. There are fewer disadvantages in having several holes in the nipple so that the milk runs freely, than in prolonging the nursing.

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TUBERCULOSIS IN INFANCY *

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It is not my purpose in this paper to do more than discuss certain limited aspects of the subject of tuberculosis in the first two years of life. The literature of tuberculosis is so enormous, and appears so complete, that it is difficult to add anything really new to our knowledge of this subject. In looking over the literature I have been impressed with the fact that in many articles the conclusions drawn are not supported by the final proof afforded by postmortem examination. This is true especially in this country, where the difficulty of obtaining permission to make postmortems on infants is so great, that it has been difficult to record observations on even a small series of cases in which final proof was obtained. The new Memorial Building of the Infants' Hospital has been open for nineteen months. During the last nine months of this time the giving of written permission for autopsy in case of death has been a necessary requirement when babies are admitted to the hospital. The increase in the number of our post-mortems under this rule has been the impetus which caused me to reopen the much discussed subject of tuberculosis.

The importance of tuberculosis as a cause of death in the first two years of life is shown by the fact that in a series of sixty-two successive necropsies, tuberculosis was found in twenty-five, and was considered the direct cause in twenty-three cases, and as the contributing cause in the other two.

THE SOURCE AND MODE OF INFECTION

Of all the subjects of discussion in connection with tuberculosis in early life, the one which has occupied most space in the literature is the question of the source of the infection, and its portal of entry into the body. This question is still one about which extremely divergent views are held. One set of writers believes that milk infected with the bovine type of bacillus is the most common cause of the disease in infancy, and

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that the most common portal of entry is the intestinal tract, or the tonsils. Another group of writers believes that the human type of bacillus is the most common cause, and that the portal of entry is usually the lungs.

The evidence brought forward in support of these two views is of varying character. Such evidence as is based on statistics of the frequency of feeding with unsterilized milk, or of the frequency of known exposure to tuberculosis is only of confirmatory value. The two most important forms of evidence bearing on this question are, first, that derived from bacteriologic study of the bacilli obtained from infants by culture or animal inoculation, and second, that derived from a careful study of the lesions found postmortem.

Based on this evidence, the reports of various investigators remain extremely contradictory. So eminent an authority as von Pirquet¹ states in his article on tuberculosis in Feer's textbook, that the human bacillus, entering through the lungs, is the cause of tuberculosis in infancy, basing his conclusions on the 1,060 careful autopsies by Albrecht, in which a primary intestinal lesion was found in seven cases only, and on the 189 necropsies of Ghon, in which all but three showed what Ghon considered a primary lesion in the lung. On the other hand Mitchell's² studies in Edinburgh showed that in 90 per cent. of the cases the bacillus was one of the bovine type.

In general the reports of postmortem findings show a greater frequency of involvement of the peribronchial and mediastinal lymph nodes than of the mesenteric. Some prominent advocates of milk infection have endeavored to explain this on the theory that the bovine bacillus can pass without causing a lesion, not only through the intestinal mucous membrane, but even through the mesenteric lymph nodes, locating itself in the lymph nodes of the chest as the point of minimum resistance. This theory I believe to be inadequately supported, and entirely untenable. It may be possible that the tubercle bacillus can enter the body of the infant without a lesion at the portal of entry; this is still an open question. But that the bacillus can skip one set of lymph nodes to locate in another, is highly improbable.

The contradictory character of the evidence as to the source of infection and mode of invasion in infantile tuberculosis can only be explained on the ground of a variation according to locality. Such variation is probably largely dependent on the character of milk supplies, and the frequency of tuberculous disease in cattle in various parts of the world. I believe that infants can be infected either with human

1. Feer: *Lehrbuch der Kinderheilkunde*, 1914.

2. Mitchell: *Brit. Med. Jour.*, 1914, No. 2768, p. 125.

bacilli, usually entering through the lungs, or with bovine bacilli, usually entering through the intestine. The present study of postmortem material therefore bears only on conditions in Boston and its vicinity.

The Primary Lesion.—Von Pirquet, in his recent textbook article, adheres to the view of Ghon, that tuberculous infection always shows a primary lesion at the portal of entry. This view is very different from the one which has been most generally accepted, which holds that the tubercle bacillus in infancy can, and usually does, pass through the tissues at the portal of entry, and then, following the lymph channels, reaches the lymph nodes, where it produces the primary lesion. This widely taught view is based on the rarity in infancy of phthisis, the chronic process most characteristic of adults, on the prominence of lymph node tuberculosis as the chronic process most characteristic of early life, and on the fact that the most prominent tuberculous lesions found in the lungs of infants are of a secondary nature. I have been inclined toward this view of tuberculosis in infancy, and have been teaching it to my students year after year.

In the recent series of necropsies at the Infant's Hospital, I determined to investigate this question of the primary lesion, by making most careful and thorough examination of the lungs and intestine in each case. It seemed possible that the primary lesion in the lung as described by Ghon and Albrecht might have been overlooked. Frequently at postmortems the lungs are examined no more carefully than by making one or two incisions in each lobe, which disclose the secondary lesions, miliary tuberculosis, or tuberculous bronchopneumonia, so prominent in infancy. It is then easy to assume that the caseous bronchial lymph nodes represent the primary lesion. In my series the lungs were cut up into the smallest fragments in the search for the primary lesion, and all suspected areas were subjected to microscopic examination.

The question of interest in this investigation was how often there would be found a lesion at the portal of entry recognizable as the primary lesion described by Ghon and Albrecht, and differing from the well-known secondary lesions.

As a result a primary lesion was actually found at the portal of entry in twenty-two of the twenty-five postmortems. The three cases in which a primary lesion was not found at the portal of entry all showed chronic tuberculosis of the bronchial lymph nodes, but none of the mesenteric lymph nodes. The nature of the primary lesion found in the lung in some cases was such as to suggest that it might easily have been overlooked, and that in the three cases a still more inconspicuous primary lesion may, in fact, have escaped observation.

Wollstein and Bartlett,³ in a study of the tuberculous lesions found postmortem in 178 infants and young children, found tuberculous areas in the bronchial lymph nodes without pulmonary involvement in seven cases, and believe that this shows that it is possible for the tubercle bacillus to pass through the lungs without localizing there. They prefer this explanation to that of Ghon, who believes that in these cases the pulmonary lesion is overlooked. As a result of my observations I am inclined to revise my views on tuberculosis in infancy, to differ with Wollstein and Bartlett's explanation, and to believe with Ghon, that it is more probable that when a primary lesion is not found at the portal of entry it is overlooked.

The Location of the Primary Lesion.—The location of the primary lesion is important as evidence of the most frequent source of tuberculous infection in infants in Boston and its vicinity. The primary lesion was found in the lung in twenty cases, and in the intestine in two cases. If we add to the twenty cases the three in which the only chronic lesions were found in the bronchial lymph nodes we have a ratio of twenty-three cases of infection through the lung to two cases of infection through the intestine. This suggests that in Boston, at least, the most frequent mode of infection is by the inhalation of tubercle bacilli from a human source, but that infection through the ingestion of bovine bacilli in contaminated milk may occur.

The Primary Lesion in the Lung.—The lesion found in the lung seemed quite easily recognizable as a primary lesion, and distinguishable from the common widespread secondary lesions. In most cases it was a circular area, varying in size from that of a pea to that of a hazlenut. The center was caseous, but usually of a grayer color than the yellowish-white caseation seen in the secondary lesions. In some there was caseous softening, or small cavities; in one there was calcification. In a few cases the primary lesion was much larger, reaching to the pleura, where its situation was marked by firm fibrous adhesions. In two of these larger lesions there were large cavities, with irregular grayish walls. Around the periphery of some of the smaller lesions were numerous miliary tubercles, suggesting direct extension. In only one case was there more than one lesion of this description.

Microscopically the primary lesion differed from caseous tubercles and secondary caseous areas in this particular, that in the latter, even when the section showed wholly necrotic tissue, the lung structure, the outlines of bronchioles and alveoli, were faintly discernible. In the primary lesion the necrotic tissue always appeared uniform and the alveolar outlines could not be made out. In only one case was there evi-

3. Wollstein, M., and Bartlett, F.: AM. JOUR. DIS. CHILD., 1914, viii, 362.

dence of healing as shown by fibrous tissue formation in the primary lesions, but this is to be explained by the fact that all the cases were fatal ones in young infants in whom the resistance was probably very low.

The situation of the primary lesion in the lung was as follows :

Left upper lobe	5 cases
Left lower lobe	0 cases
Right upper lobe	8 cases
Right lower lobe	5 cases
Right middle lobe	2 cases

The favorite situations were at the apex and near the hilus.

The Primary Lesion in the Intestine.—The lesion found in the intestine in two cases, and considered primary, was a tuberculous ulceration. In one case there was a single ulcer, while in the other case the ulcers were multiple. There was nothing about the appearance of these ulcerations differing from that seen in the secondary ulcerations found in several cases. My reasons for believing the intestinal ulceration to be a primary lesion in these two cases are, first, because in them the mesenteric lymph nodes *only* were tuberculous, and they were the only cases in which tuberculosis of the mesenteric lymph nodes was found without tuberculosis of the bronchial lymph nodes. As additional evidence, one of these cases was one of a series known to have occurred in a limited locality, and all having the same milk supply. Furthermore, animal inoculation from this case gave a bovine type of bacillus.

Involvement of the Lymph Nodes.—The bronchial lymph nodes were found tuberculous in the twenty cases having a primary lesion in the lung, and in three cases in which no primary lesion was found. They were involved alone in sixteen cases, including the three without evident pulmonary lesion. The mesenteric lymph nodes were tuberculous in addition to the bronchial lymph nodes in seven cases having a primary lesion in the lung, and were involved alone in the two cases having a primary lesion in the intestine.

Secondary Ulcers of the Intestine.—Tuberculous ulceration of the intestinal mucous membrane was found in seven cases beside the two in which this lesion was considered primary. In all cases the ulcers were multiple. My reasons for believing these lesions to be secondary are the following: 1. In all the seven cases a primary lesion was found in the lung. 2. In all of them there was tuberculosis of the bronchial lymph nodes, which in most cases appeared to represent a more advanced and older process than that in the mesenteric lymph nodes. 3. In all of them there was evident in the primary pulmonary lesion either caseous softening, or cavity formation, and conversely, in

no case in which such a condition was found in the primary lesion did I fail to find ulceration in the intestine. I believe it to be a probable conclusion that these tuberculous ulcerations of the intestine are secondary to swallowed tuberculous material coughed up from the softening of the primary lesion.

These seven cases with secondary tuberculous ulceration of the intestine were identical with the seven cases in which the mesenteric lymph nodes were involved in addition to the bronchial lymph nodes. This is a finding of the greatest importance in connection with the question of the ability of the tubercle bacillus to pass through the mucous membrane without causing a lesion at the portal of entry. In all there were nine cases in which the mesenteric lymph nodes were found to be tuberculous, and in all of them there was also found tuberculous ulceration of the mucous membrane of the intestine. There was no case in my series showing tuberculosis of the mesenteric lymph nodes without an intestinal lesion. In two cases the intestinal lesion was primary; in the other seven secondary to a primary lesion in the lung, from which tuberculous material was swallowed. I believe these findings to be evidence against the view of the ability of the tubercle bacillus to pass through the intestinal mucosa without leaving traces of its progress in the form of a definite lesion.

Other Secondary Lesions.—Chronic tuberculosis of the lymph nodes was found in every case. Most of the other secondary lesions were of an acute character. A more or less generalized miliary tuberculosis, or tuberculous meningitis was found in twenty-three cases. In two cases were chronic lesions only found. Tuberculous peritonitis was found in two cases. Solitary tubercle of the brain was found in one case.

The secondary lesions found in the lung were of two distinct kinds. One was a tuberculous bronchopneumonia characterized by exudate into the pulmonary alveoli, with more or less necrosis or caseation. This lesion was found in ten cases, and I believe it to represent an extension of the tuberculous process from the primary lesion to the lung through the bronchial channels. The other secondary lesion found in the lungs was a miliary tuberculosis, which both in macroscopic and microscopic appearance differed entirely from the tuberculous bronchopneumonia just described. The lesion consisted of numerous sharply defined miliary tubercles without any exudate into the surrounding alveoli. This was the sole secondary lesion found in the lung in thirteen cases. But such miliary tubercles were also found in a certain number of cases in which tuberculous bronchopneumonia was the most prominent lesion. This lesion probably represents extension of the tuberculous process from either the primary lesion or some sec-

ondary lesion through the medium of the general circulation, forming part of a general miliary tuberculosis. Twenty-three of the twenty-five cases showed miliary tubercles in various parts of the body.

The brain was not examined in three cases, and no lesion of the meninges was found in two cases. In nineteen cases a tuberculous meningitis was found, which was the immediate cause of death. In thirteen of these cases the meninges showed small miliary tubercles without evidence of exudate. In six cases, in addition to the miliary tubercles there was more or less cellular or fibrinous exudate along the course of the vessels.

Bacteriological Findings.—In only five cases in this series were animal inoculations made to determine whether the infection was with a human or with a bovine type of bacillus. The bovine type was found in one case, and the human type in four cases. The case in which the bovine type of bacillus was found was one of those having a primary lesion in the intestine and the one known to have been fed with contaminated milk. The four cases in which a human type of bacillus was found included one of the cases in which there was no apparent primary lesion. The cases in which the type of bacillus was tested by animal inoculation are too few to afford more than confirmatory evidence of the greater frequency of infection from a human source.

Previous Feeding.—The previous feeding of these patients was as follows: Fourteen babies had had milk of an unknown or doubtful character. Five babies had been fed exclusively on a milk considered to be of the best character. Six babies had been exclusively breast fed.

Exposure to Tuberculosis.—In four cases only was there a definite history of exposure to tuberculosis obtained. In a few others there was suspicion of such exposure.

THE DIAGNOSIS OF TUBERCULOSIS IN INFANCY

In this series of cases a diagnosis of the tuberculous nature of the disease was made during life in twenty-three out of twenty-five cases. This does not mean that the diagnosis of tuberculous infection in infancy is easy, or that it can be made in so large a number of cases. It must be remembered that these were all fatal cases, seen in the last stages of the disease. In fifteen of them a diagnosis was possible because they showed the definite clinical picture of tuberculous meningitis with characteristic cerebrospinal fluid. The two cases in which the diagnosis was not made were apparently cases of chronic nutritional disturbance with atrophy. One of them is particularly interesting. The child was treated in the hospital for some weeks as a feeding case and did very well, gaining weight steadily. At no time during its stay in hospital did it show any symptoms suggesting tuberculosis, nor did

it have any fever. Within twenty-four hours of its discharge from the hospital it had a series of convulsions followed by death. It was brought back for necropsy and showed extensive chronic tuberculosis of the bronchial lymph nodes with acute miliary tuberculosis of all the organs of the body, but none of the meninges. I am inclined to doubt if acute miliary tuberculosis can often be diagnosed in infancy unless the brain is involved.

The principal diagnostic feature in this series of cases was due to the existence of a tuberculous meningitis. The important question is, whether tuberculosis could have been recognized before the onset of this acute manifestation? For this is an important point in the treatment of the disease.

There are three important points beside the existence of such definite manifestations as tuberculous meningitis or tuberculous peritonitis, on which the diagnosis of tuberculosis in infancy is based. These are: 1. The finding of physical signs suggesting tuberculosis in the chest. 2. The evidence given by the tuberculin reaction. 3. The evidence by Roentgen-ray examination of the chest. An effort was made at the Infants' Hospital to carry out as thoroughly as possible these three methods of investigation, but owing to the fact that many babies were brought in in a moribund condition and died so soon after admission, the records have been very incomplete.

Physical Signs in the Lungs.—The physical examination of the lungs for signs suggesting tuberculosis gave the following results:

Positive	14 cases
Negative	11 cases

In four of the fourteen positive cases d'Espine's sign was the only one found. In the other ten cases evidences of consolidation in various parts of the lung were found which were of such a character as to suggest the possibility of tuberculosis, even if tuberculous meningitis had not also been present. In comparing the physical signs with the postmortem findings the following points were striking: 1. Acute miliary tuberculosis of the lung without tuberculous bronchopneumonia appears to give no recognizable physical signs in the lung. 2. Tuberculous bronchopneumonia usually does give recognizable physical signs in the lungs. In some cases only scattered râles are found; in others there are signs of consolidation in various parts of the chest. The infants may or may not show the appearance of bronchopneumonia with rapid breathing, etc. 3. The presence of d'Espine's sign in infancy usually means tuberculosis of the bronchial lymph nodes, but this sign may not be obtained in cases in which the glands are found enlarged at necropsy. 4. The primary lesion gives no recognizable physical signs in the chest,

unless very large, and in such a case the signs are only those of consolidation and are indistinguishable from tuberculous bronchopneumonia.

The Tuberculin Reaction.—Only the von Pirquet cutaneous reaction was employed. The results were as follows:

Positive	6 cases
Negative	12 cases
Not done	7 cases

The large number of negative reactions in cases proved to be tuberculosis is striking. It must be remembered, however, that many of the patients in the series were acutely ill, and that the reaction was observed very shortly before death, when resistance to the infection was probably at a minimum. It is possible that the results obtained in this series of cases has little bearing on the value of the reaction in cases not in the acute stage of the disease. Nevertheless, one of the chronic cases showed a persistently negative reaction, while in some of the most acute cases a positive reaction was observed within a very short time before death. On the whole, I am inclined to believe that the value of the cutaneous tuberculin reaction in infancy is not so great as many writers and statistical reports would lead us to suppose. A negative reaction seems to be a frequent finding in any stage of the disease, and gives no evidence at all. A positive reaction on the other hand, in infancy, means tuberculosis. For some time at the Infants' Hospital a routine von Pirquet test has been made on every case. We have yet to see a case in which a positive reaction has accompanied a negative post-mortem finding. There was no case in this series in which a positive von Pirquet would have been the only means of diagnosis, if found at a time preceding the acute stage of the disease. There was one case in which the diagnosis rested on a positive von Pirquet with a positive d'Espine's sign.

Roentgen Ray Examination of the Chest.—This was made in thirteen cases of the series, and was positive in every case. There were several cases in which it gave the only positive finding. In general there was a surprisingly close correspondence between the Roentgen-ray picture and the postmortem findings. The enlargement of the bronchial lymph nodes could be made out in most of the cases. Tuberculous bronchopneumonia was correctly diagnosed from the Roentgen-ray in several cases, but not in all those in which it was found postmortem. The primary lesion was not shown, when small, but was conspicuous when very large. Miliary tuberculosis of the lung without tuberculous bronchopneumonia was not shown.

There were two cases in the series in which before the acute stage the diagnosis could have been made from the Roentgen-ray picture

alone, and two cases in which d'Espine's sign was positive, but in which the diagnosis of the pulmonary condition rested chiefly on the roentgenogram.

The table shows the occurrence of the three forms of diagnostic evidence in the series:

CERTAIN DIAGNOSTIC SIGNS IN TWENTY-FIVE CASES OF TUBERCULOSIS IN INFANCY, COMING TO NECROPSY

Clinical Type	Roentgen Ray	Signs in Lung	Von Pirquet
1. Tb. peritonitis	?	0	?
2. Atrophy	?	0	?
3. Tb. meningitis.....	?	0	?
4. Tb. meningitis.....	?	0	?
5. Malnutrition	+	d'Espine only	0
6. Bronchopneumonia	+	+	0
7. Tb. meningitis.....	?	0	?
8. Tb. meningitis.....	?	0	0
9. Tb. meningitis.....	+	+	+
10. Tb. meningitis.....	?	+	+
11. Tb. meningitis.....	+	0	0
12. Tb. meningitis.....	+	0	0
13. Tb. meningitis.....	+	d'Espine only	?
14. Chronic tuberculosis of lung.....	+	+	0
15. Tb. meningitis.....	?	d'Espine only	+
16. Tb. meningitis.....	+	+	+
17. Tb. meningitis.....	?	0	0
18. Bronchopneumonia	+	+	0
19. Bronchopneumonia	?	0	?
20. Tb. meningitis.....	+	+	+
21. Chronic tuberculosis of lung.....	+	+	+
22. Tb. meningitis.....	+	+	0
23. Atrophy	?	0	0
24. Tb. peritonitis.....	+	+	0
25. Tb. meningitis.....	?	+	0

TYPES OF HYDROCEPHALUS—THEIR DIFFERENTIATION AND TREATMENT *

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The physiology of the cerebrospinal fluid, its origin, secretion and absorption, has been the object of intensive study during recent years.¹ The subject has been studied from many angles and by many observers, and the information thus afforded has opened a new vista into the diseases of the central nervous system, in which the cerebrospinal fluid plays an important part. It has been proved conclusively that the cerebrospinal fluid is, for the most part, at least, a secretory product of the choroid plexus. We have found, moreover, that the secretory activity of this gland may be influenced by certain factors, and in the course of our investigations it was found that thyroid extract had a distinctly *inhibitory* effect on the output of cerebrospinal fluid—a fact which may be of real practical importance in the treatment of conditions in which excessive secretion is the disturbing element. Many theories have been advanced as to the exact mode of absorption, but complete unanimity of opinion has not as yet been reached. Certain it is, however, that all abnormal accumulations of fluid within the ventricles are due to a loss of balance between secretion and absorption, the underlying factors being an obstruction to the outflow of the fluid from the ventricles, delayed or defective absorption, or a hypersecretion.

Of all the conditions in which the excessive accumulation of fluid has to be reckoned with, e. g., meningitis, brain tumor, and hydrocephalus, the latter alone, will be considered in this paper. The time has come to throw aside the crude classification of all forms of hydrocephalus, into internal and external: internal hydrocephalus clearly

* Submitted for publication Nov. 4, 1915.

1. The reader is referred to the contributions of Dixon and Halliburton, Thomas, Dandy and Blackfan, Weed and Cushing, and of Frazier and Peet as follows:

Frazier, C. H. and Peet, M. M.: Factors of Influence in the Origin and Circulation of the Cerebrospinal Fluid, *Am. Jour. Physiol.*, 1914, xxxv, 3; The Action of Glandular Extracts on the Secretion of Cerebrospinal Fluid, *Ibid.*, 1915, xxxvi, 4; Influence of Diiodotyrosine and Iodothyrene on the Secretion of Cerebrospinal Fluid, *Ibid.*, 1915, xxxviii, 1.

Frazier, C. H.: The Cerebrospinal Fluid in Health and Disease, *Jour. Am. Med. Assn.*, 1915, lxiv, 1119.

enough an obstructive form, and external hydrocephalus everything and anything not included in the "internal" variety. From our investigations, therefore, we venture to suggest a new classification, having a physiologic background with direct clinical application:

- I. Hydrocephalus obstructivus.
- II. Hydrocephalus nonabsorptus.
- III. Hydrocephalus hypersecretivus.
- IV. Hydrocephalus occultus.

I. In *Hydrocephalus obstructivus*, the internal hydrocephalus of the old nomenclature, there is mechanical obstruction to the natural drainage of the cerebrospinal fluid from one or more ventricles into the subarachnoid space, where the absorption takes place. This obstruction may be due to a congenital defect, such as absence of the aqueduct of Sylvius, or as is more frequently the case, it may be the result of adhesions from a preexisting inflammatory lesion. If the aqueduct of Sylvius is lacking or closed by adhesions, there will be a dilatation of both the third and the lateral ventricles, while a closure of the forearm of Munro would cause merely an enlargement of the lateral ventricle on the affected side. If, as is often true in cases of high-grade, but evenly-distributed hydrocephalus, the passage of the fluid through the foramina of Magendie and Luschka is blocked, there will be a general dilatation in which all the ventricles participate. While we now know that obstruction is not responsible for as large a number of cases of hydrocephalus as was formerly supposed, nevertheless it has been proved conclusively both by necropsy findings, and by the experimental production of hydrocephalus through occlusion of the aqueduct of Sylvius, that obstruction is one of the causative factors. Too great emphasis, however, can scarcely be laid on the importance of differentiating *Hydrocephalus obstructivus* from the other types in which the passageways from the ventricles are patulous.

II. In *Hydrocephalus nonabsorptus*, absorption is delayed or defective as has been proved by the phenolsulphonephthalein test. Whether the restricted absorption is to be attributed to (1) the cutting off of part of the subarachnoid space by adhesions, (2) a toxic substance in the fluid which prevents its absorption by the venous channels, or (3) whether it is due to an abnormal condition of the agents—whatever we grant them to be—which transport the fluid to the venous circulation, is still a matter of conjecture. Since the cerebrospinal fluid is absorbed by the venous channels, it is quite possible that an obstruction to the venous circulation, such as thrombosis, might be responsible for the delayed absorption. Indeed, Dandy and Blackfan succeeded in producing a low-grade experimental hydrocephalus by ligation of the vena galena magna. But we cannot entirely eliminate

the possibility of a change in the character of the fluid itself or an abnormal condition of the conveyors of the fluid to the venous circulation until there have been more pathologic examinations, and more chemical, bacteriologic and cytologic examinations of the fluid in this type. However this may be, *Hydrocephalus nonabsorptus* should be carefully differentiated from the other forms that an effective means may be instituted for draining the fluid to other areas where it may be absorbed.

III. By a process of elimination and by a careful consideration of the normal physiology of the cerebrospinal fluid and of the possible changes under abnormal conditions, the third type with apparent excessive accumulation of fluid has been attributed to hypersecretion—*Hydrocephalus hypersecretivus*. Since it has been conclusively proved by morphologic and histologic studies of the choroid plexus, by chemical analyses of the fluid, by a study of the effect of choroid extract on the secretion of cerebrospinal fluid, that the cerebrospinal fluid is the secretory product of the choroid gland, it would seem logical to suppose that a pathologic condition of the gland itself or a toxic substance in the fluid coming in contact with the plexus might bring about a hyperactivity of its cells. To establish this fact beyond the peradventure of a doubt will require the examination of many choroid plexuses and bacteriologic examination of the fluid in a large number of cases. I am now carrying on some studies in regard to the histology and pathology of the plexus which I trust will throw some light on the etiology of this type.

IV. With propriety we include in the varieties of hydrocephalus this fourth type, for which the term *Hydrocephalus occultus* has been chosen, which though paradoxical, is otherwise appropriate. The condition thus designated occurs usually in children, though occasionally in adults, and is characterized by excess of fluid in the ventricles, basal cysternae, and sometimes throughout the subarachnoid space, without necessarily any increase in the cranial dimensions. Symptomatically, this condition may be more closely allied to tumors, but from the point of view of treatment properly belongs to the problems of hydrocephalus in that the essential feature is an excessive accumulation of cerebrospinal fluid in the subarachnoid space. To illustrate this type, I may cite the following case:

A 3-year-old boy was referred to my service at the University Hospital, Oct. 17, 1911, by Dr. J. P. Crozer Griffith (File No. 10384). He was one of four children, two of whom had died in infancy. There was no evidence of injury at birth. September, 1911, the child fell down stairs, without apparent injury, but one week later developed convulsions and since that time has had seven or eight seizures. The child complained of headache a great deal, and had vomited frequently. A thorough physical examination failed to reveal any focal symptoms suggestive of intracranial tumor, with the exception of

the fact that the gait was a trifle unsteady, and in the movements of his arms as in feeding himself, there was some uncertainty or wavering. The latter might have been due to his defective vision. There was a papilledema of both disks, and vision was almost lost.

In the hope of saving at least a residuum of sight, pending the localization of a suspected tumor, a subtemporal decompression was performed. A considerable quantity of fluid was evacuated, and soon after the operation a large hernia cerebri developed, apparently under great tension. Evidently the hemisphere had been displaced by the distending ventricle.

It was not long before the papilledema subsided, revealing a well-marked, post papillitic atrophy. The convulsions ceased, the other evidences of intracranial tension disappeared, and but for the fact that vision remained impaired, the child's health was restored, and at an examination made three years later, the child was in perfect health.

An interesting feature in this case was the gradual subsidence of the hernia cerebri from one of large dimensions under terrific tension, to one of very moderate size. My interpretation of this striking change in the condition of intracranial tension was that the normal balance between the absorption and secretion of cerebrospinal fluid had been restored. The degree of optic atrophy indicated very positively that the duration of the primary lesion was very much longer than would be inferred from the history, that is, more than a matter of a few weeks. It was not until the intracranial tension had developed to the point of causing headache, vomiting and convulsions that the mother sought medical advice. Had the subtemporal decompression been performed before the stage of optic atrophy, the child's vision would have been preserved.

It will be seen at a glance that the proposed classification differs essentially from the venerable classification, internal and external hydrocephalus, and has a definite pathologic and physiologic basis. For practical consideration, therefore, it is now incumbent on the practitioner, before treatment is begun, to apply the tests which have been elaborated for distinguishing one from the other.

TEST 1.—These tests² are based on the application to the cerebrospinal fluid of the phenolsulphonephthalein test for renal function. As the slight alkalinity of the commonly used solution is irritating to the brain and cord, a neutral solution is used. The solution is prepared in ampules containing 1 c.c. of the neutral solution. Under normal conditions, when the dye is injected into the lateral ventricle, it should appear in the fluid withdrawn by lumbar puncture within three to eight minutes. If therefore, after injection the fluid from the spinal canal is not stained within the specified time, it may be assumed that the drainage of the ventricles has been interrupted, and that we are dealing with hydrocephalus obstructivus.

Furthermore, it has been proved conclusively, first that the quantity of cerebrospinal fluid absorbed within the ventricles, if any, is a negligible quantity; and secondly, that from 30 per cent. to 60 per cent. of phenolsulphonephthalein should, under normal conditions, be secreted by the urine within the first two

2. These tests have been elaborated independently by Blackfan and Dandy and by Frazier and Peet, and the results are in entire accord.

hours. If, therefore, 1 c.c. is injected into the ventricle and the amount secreted by the first two-hour urine specimen estimated, we have at once additional evidence that we are dealing with the obstructive type.

The same test may be applied in the more unusual type of unilateral hydrocephalus. After the dye has disappeared from the urine following the test of one ventricle, the test may be applied to the other.

TEST 2.—From a lumbar puncture needle, 1 c.c. of cerebrospinal fluid is allowed to escape. A 2 c.c. record syringe, containing exactly 1 c.c. of the neutral phenolphthalein solution is attached to the lumbar puncture needle, and the piston withdrawn until the syringe is full. The solution of dye thus diluted is slowly injected into the subarachnoid space; the time of injection is noted and in five minutes a specimen is tested for the dye, and the entire amount of urine secreted in two hours collected. In the normal, a trace of the dye should appear in ten minutes and the entire amount excreted within the first two hours. Any marked diminution in the time or deviation from the amount indicates delayed absorption. In a case in which this test was recently applied, I saw the child when he was 16 months old in consultation with Dr. T. B. Holloway of Philadelphia. (History File No. 28358.) The delivery had been by forceps, the confinement lasted six hours, and after birth two lumps were noticed in the parietal region. Examination revealed the gross characteristics of hydrocephalus; the circumference of the head was 24 inches, and the anterior fontanel measured 2 by $4\frac{1}{2}$ inches. The Wassermann reaction both on the spinal fluid and the blood was negative. The intraspinal pressure was 40 mm. of mercury. The child's mentality was not affected, except in so far that he had not begun to talk. He appeared intelligent and was well nourished.

June 30, 1915, a test for absorption from the subarachnoid space was made by Dr. M. M. Peet. Phenolphthalein appeared in the urine ten minutes after injection; within the two-hour period the total excretion was only 15 per cent. (delayed absorption). The test for ventricular drainage was made July 5, 1915. One cubic centimeter of the neutral phenolsulphonephthalein was injected into the ventricle. On lumbar puncture the dye did not appear until twenty minutes, and then only after the withdrawal of 120 c.c. of fluid. The fluid was withdrawn at five minute intervals, and twenty-five minutes after the injection, a slightly stronger trace appeared. The slowness with which the dye appeared in the cerebrospinal fluid, points to an obstruction, although not complete, of the ventricles. The fact that so large an amount of cerebrospinal fluid was found without the ventricles suggests that the obstruction was at the aqueduct of Sylvius, and that the excess of cerebrospinal fluid was secreted in the fourth ventricle. Evidently we were dealing with a hydrocephalus chiefly of the obstructive type, and to meet this condition I advised puncture of the corpus callosum. This was carried out by my assistant, Dr. L. H. Landon, July 6, 1915, and he made the observation at the time of the operation, that the fluid in the ventricles was still stained with the dye. This was rather interesting, in that it showed quite conclusively, that there must have been a very positive obstruction to the free circulation of the cerebrospinal fluid. The child was dismissed from the hospital in excellent condition, and thyroid feeding resumed.

If we are dealing with the internal or obstructive type, the absorption of phenolsulphonephthalein from the subarachnoid space and the excretion by the kidney is practically normal. If on the other hand, we are dealing with the nonabsorptive type, the time of appearance of the dye in the urine is delayed and it may not appear for an hour or more, and the amount secreted in the two hour period is correspondingly low; frequently but a trace is detected. In a few cases no phenolsulphonephthalein reaches the urine in four or six hours.

SUMMARY OF CLINICAL TESTS

First examination:

1. Lumbar puncture.
2. Withdrawal of 1 c.c. of cerebrospinal fluid.
3. Attach 2 c.c. record syringe filled with 1 c.c. neutral solution of dye.
4. Withdraw piston until syringe is full.
5. Inject solution slowly into lumbar subarachnoid space.
6. Withdraw needle.
7. Test urine for phenolsulphonephthalein every 5 minutes until dye is detected.
8. Estimate total amount of dye excreted in the first two-hour specimen of urine.

Second examination (following day, or after dye is no longer found in urine):

1. Puncture of the lateral ventricle.
2. Inject 1 c.c. neutral phenolsulphonephthalein solution.
3. Lumbar puncture. Examine for dye every five minutes until dye appears.
4. Test five-minute specimens of urine.
5. Estimate total amount of dye excreted in first two-hour specimen.
6. In calculations, the amount of dye lost by lumbar puncture must be taken into consideration.

TREATMENT

It is not the purpose of this paper to enter into any detailed discussion of the treatment of hydrocephalus. To do so in extenso would necessitate opening the pages of medical history at the time when Hippocrates boldly tapped the hydrocephalic ventricle, and carrying the reader on numberless surgical flights and falls. The number of operations that have been devised to grapple with this Charybdis of surgical endeavor are conspicuous more for their ingenuity than for their life-saving accomplishment. To record here the mortality of many operations for hydrocephalus would be too depressing and would dampen the ardor of those seeking to shed new light.

An attempt will be made merely to suggest methods of treatment, and in doing so to keep within the bounds of reasonable risk and promising results.

I realize, of course, that the excessive accumulation of fluid in the hydrocephalic may not be the only pathologic factor, and that the ability to cope with this may not be the key to final and complete restoration of health. At the same time, it is reasonably certain that the excessive accumulation of cerebrospinal fluid is the dominant disturbing element of this disease, and must be given consideration.

The suggestions as to treatment will be made to conform with our classification, on the ground that different etiologic factors indicate differing therapeutic methods. The simplest and most effective method of dealing with hydrocephalus obstructivus is puncture of the corpus callosum, the *Balkenstich* of Anton and Bramann. This operation is in hydrocephalus devoid of difficulty, and in the simplest way provides an outlet for the pent-up fluid into the subarachnoid space, where

it may be absorbed. Because of its simplicity and effectiveness, it should supplant all methods of ventricular drainage; drainage by gold or platinum tubes, drainage into the longitudinal sinus, drainage into the jugular veins, drainage of the fourth ventricle, etc.

In the nonabsorptive type, greater technical difficulties are encountered. Speaking now with some reservation, because my technic for this is in the development stage, I venture to recommend the establishment of a drainage tract into the pleural cavity. The distance is not too great, the anatomic features are adaptable, and the pleural cavity is a convenient and readily accessible reservoir.

When the lesion is due to hypersecretion I resort to thyroid feeding. In the numerous experiments which we made on the activity of the choroid plexus, as a secretory organ, at once the most conspicuous and impressive finding was the influence of thyroid feeding. Subjected to every possible test in the elimination of sources of error, it was found that thyroid invariably acted as a depressor on the choroid plexus, and invariably reduced the secretion of cerebrospinal fluid. This reduction was notable in amount, in constancy and in duration. In some instances the experiments covered periods of five consecutive hours. With this evidence of what appears to be an almost specific influence of thyroid extract on the choroid plexus—as it were, an interglandular relation—I began to apply the treatment in appropriate cases. To the pediatricist, who is brought in contact with these cases in much larger numbers than the surgeon, I hope this line of treatment may appeal sufficiently to give it a thorough trial, and, by the results, to establish or disestablish it as an approved method. In the case of a baby which I saw June 13, 1914, in consultation with Dr. G. R. Anderson, thyroid feeding was inaugurated. The baby, at that time 5 weeks old, was the first child of apparently healthy parents. Labor was not instrumental, but the head was engaged in the birth canal over an hour. At the time of birth the child seemed in every way to be normal, and it was not until two weeks after birth that the doctor's and parents' attention was called to the fact that the size of the head had increased disproportionately to the natural growth. At the time of my examination, the child appeared thin and poorly developed. There were no other congenital defects. The head was unquestionably large, larger than it should have been for a child of that age and size, the forehead prominent and unusually large. The circumference of the head was $16\frac{5}{8}$ inches, and from a point in front of the external auditory meatus on one side, to a similar point on the other, measured $12\frac{1}{4}$ inches. The question of operation, of course, never came up for consideration. I was constrained to give an unfavorable prognosis, in view of the fact that the child's head had increased in size so rapidly

in the first few weeks of its existence. Based entirely on our observations in the laboratory, I advised the administration of thyroid extract beginning in doses of 1/6 gr. and gradually increasing the dose up to the point of tolerance.

July, 1915, the physician attending reported that the fontanelles had closed, that there had been no disproportional increase in the circumference of the child's head, that the child had begun to talk and walk with assistance, and that apart from an internal squint, the child seemed perfectly well and normal. Whatever may have been the influential factor, the disease had been arrested.

This brief sketch of the causes and treatment of hydrocephalus it is hoped will stimulate physicians to take up anew this old vexing problem, to subject their cases to a more critical analysis for the differentiation of one type from another, and to be influenced in management and treatment by the more recent contributions to our knowledge of this disease, not losing sight of the fact that experimental evidence points very convincingly to a retarding influence of thyroid extract on the secretory activity of the choroid plexus.

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METABOLISM STUDIES IN HEMOPHILIA*

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Since the year 1820 when Nasse of the University of Bonn formulated the law that males alone are the bleeders, and the disease, hemophilia, is transmitted by normal females through their marriage with normal males, much has been written on the subject of hemophilia. This disease, which Grandidier termed "The most hereditary of hereditary diseases," has been discussed from all angles and points of view, and the only conclusion that has been reached is that the coagulation of the blood was defective (Wright, Addis, et al.).

What the cause of this delayed coagulation is has been explained in various ways. Sahli and Morawitz have stated that the calcium content of the blood is normal in this disease; that the thrombogen content of the blood is normal; and they ascribe the delayed coagulation to a deficiency in the thrombokinase (the activator of the thrombogen) of the blood. This theory has been contradicted by Addis, who believes that the fault lies in the composition of the thrombogen, which (though normal in quantity) is so changed in character that it liberates the thrombin with difficulty.

According to Weil, the delayed clotting is due to an excess of anti-thrombin, whereas, according to Howell the deficiency of the blood in thrombogen is to be blamed for the defect. It was Wright who ascribed the delayed coagulation of the blood in hemophilic subjects to a lack of calcium.

In examining the literature on this subject I have failed to find any records of metabolism studies in this condition. Since I have had occasion to make such studies of two cases of hemophilia, I think it will be interesting to report my results.¹

The two cases studied were of different types of hemophilia. They were both in boys. Julius was about 9 years old, and gave a typical history of hereditary hemophilia. The boy Alter, was about 6 years old and was not a hereditary "bleeder." Dr. Hess thus presents the clinical history of this boy (Alter):

The child has been under our observation for the past three years. . . . Attention was first directed to him on account of his tendency to bleed from

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1. The clinical studies of these cases were reported by Dr. A. F. Hess, Johns Hopkins Hosp. Bull., 1915, xxvi, 372. A preliminary communication was made by A. F. Hess and Max Kahn, Biochem. Bull., 1915, iv, 213.

minor cuts, to manifest frequent "black-and-blue marks" and to have severe hemorrhages from the nose. As far as can be ascertained, he is the sole member of his family who is a bleeder, so that we must consider him as affording an instance of the sporadic type of hemophilia. He is fairly well nourished, weighs about 50 pounds and shows no other abnormality except a moderate degree of ichthyosis of the skin.

In both of the cases it was found that there was delayed coagulation of the blood. In the case of Julius the blood clotted in about eighteen minutes, and in the case of Alter it clotted in thirty-four minutes. On analyzing the blood of these patients for calcium and comparing the results with normal cases we obtained the results shown in Table 1:

TABLE 1.—CALCIUM OXID IN BLOOD

Normal Controls, Gm.	Alter, Gm.	Julius, Gm.
0.072.....	0.047	0.068
0.068.....	0.056	0.069
0.074.....	0.058
0.066.....	0.068
0.071.....	0.062*
0.073.....	0.064*
0.062.....
0.068.....
0.075.....
0.069.....
0.075.....
0.065.....

* Calcium lactate (2 gm.) had been given for the previous three days by mouth.

It will be seen that in the case of Julius, atypical hemophilic, the lime in the blood was normal, whereas in the case of Alter the calcium content of the blood was decreased.

We reasoned that if the calcium deficiency was the sole cause of the failure of the blood to clot in the case of the boy Alter, this defect could be remedied by adding to the blood the missing lime salt. We, therefore, prepared a solution of calcium chlorid in physiologic saline (0.04 gm. Ca calculated from CaCl_2 in 1,000 gm. saline) of such strength that the addition of a drop of this solution to ten drops of blood will approximately supply the deficiency in calcium. (Normal CaO in blood calculated to be 0.08 parts per thousand). Table 2² shows the effect of the addition of the calcium solution on the clotting

2. Hess, A. F.: Johns Hopkins Hosp. Bull., 1915, xxvi, 373.

TABLE 2.—EFFECT ON CLOTTING TIME OF BLOOD OF ADDITION OF CALCIUM CHLORID SOLUTION

A. NORMAL CASE

Clotting Time	Control	Drops of Ca Solution added			
		1	2	3	4
4 min.	+	+	+	+
5 min.	++	++	++	+
6 min.	+++	+++	++	++
7 min.	++	++
9 min.	++	++
11 min.	++	++
13 min.	++	++
15 min.	+++	++
17 min.	++

B. HEMOPHILIA CALCIPRIVA (ALTER).

5 min.	—	—	—	—	—
9 min.	—	—	—	—	—
11 min.	—	+	++	—	—
13 min.	—	+	+++	+	—
17 min.	—	+++	++	+
21 min.	—	++	++
26 min.	+	+++	+++
34 min.	+++

C. TYPICAL HEMOPHILIA

4 min.	—	—	—	—	—
8 min.	—	—	—	—	—
10 min.	+	++	+	++	+
14 min.	++	++	++	++	++
18 min.	+++	++	++	++	++
22 min.	++	++	++	++
26 min.	++	+++	++	++
30 min.	+++	++

+++ denotes complete clotting time.

time of the blood. The determinations of the coagulation time of the blood were made by Dr. A. F. Hess. This table is taken from Dr. Hess' report.

It will be observed that in the normal case the addition of two drops of the lime solution had no effect, and the addition of three and four drops delayed the coagulation. In the case of Alter the addition of one drop quickened coagulation from thirty-four minutes to seventeen minutes; the addition of two drops caused clotting in thirteen minutes; the addition of three and four drops again slowed coagulation to twenty-six minutes. In the case of Julius the addition of calcium chlorid slowed the coagulation of the blood.

Having observed these effects we thought it advisable to study the general metabolism of the two hemophilic children, and compare them with normal children. The following procedure was adhered to in the study of the metabolism.

Both patients were fed on a diet of milk, eggs, butter and bread. Duplicate samples of each substance given the patients were sent daily to the laboratory where they were weighed and analyzed. The urine and the feces were collected daily for examination.

The experiment may be divided into three periods: 1. A fore-period, of a duration of three days, during which time the patients were kept in bed and fed the diet above mentioned, without being given any medication. 2. A calcium-feeding period also lasting for three days, from August 19 to 22, 1914 (during this time the patients received daily 2 gm. of calcium chlorid and 1 gm. of magnesium oxid). 3. An after-period, lasting three days, during which time there was given no medication.

EXPERIMENTAL METHODS

In the analysis of the food the following methods were employed: Nitrogen by the Kjeldahl method; total sulphur by the Wolff and Osterberg method, a modification of the Benedict method; calcium and magnesium by the McCrudden method, after ashing and extracting the ash with hydrochloric acid; phosphorus by the Neumann method.

In the urinary analyses, in addition, ammonia was determined by the Folin method, urea by the Benedict method, and total and ethereal sulphates by the Folin method. The inorganic sulphates were computed by subtracting the ethereal sulphates from the total sulphates, and the neutral sulphur by subtracting the total sulphate sulphur from the total sulphur. Total phosphorus was determined by the Neumann method, the phosphorus being weighed as magnesium pyrophosphate; creatin and creatinin by the Folin method, and uric acid by the Krieger-Schmidt method.

For the feces the same methods were used. In the case of the fat the Kumagawa and Suto method was employed. The results of the examinations are summarized in the four accompanying tables (Tables 3, 4, 5 and 6). These show that the disturbances of nutrition are not at all similar in the two children. In order to appreciate the results we have obtained it is wise to compare them with the metabolism of normal children, and we take the case of Herman S., a boy 5 years of age, as a standard (Tables 7 and 8).

TABLE 3.—SUMMARY OF METABOLISM DURING THE THREE PERIODS
A. TYPICAL HEMOPHILIA (JULIUS)

Substance	Fore Period (Average per Diem)				Feeding Period (Average per Diem)				After Period (Average per Diem)			
	Food	Urine	Feces	Bal.	Food	Urine	Feces	Bal.	Food	Urine	Feces	Bal.
Nitrogen.....	16.14	10.55	3.75	+1.84	16.10	10.18	2.28	+3.69	14.61	10.38	1.93	+2.30
Sulphur.....	1.90	0.98	0.87	+0.05	1.98	0.91	0.95	+0.07	2.06	0.91	0.95	+0.20
Phosphorus..	3.78	2.13		+1.65	3.26	3.08		+0.23	3.79	2.51		+1.28
Chlorin.....	7.94	6.74		+1.20	9.19	8.17		+1.02	8.58	6.78		+1.80
Calcium.....	1.59	0.206	0.824	+0.56	3.39	0.466	2.08	+0.85	1.47	0.17	0.71	+0.59
Magnesium...	0.51	0.177	0.183	+0.20	1.64	0.84	0.61	+0.19	1.45	0.70	0.53	+0.22

B. HEMOPHILIA CALCIPRIVA (ALTER)

Nitrogen.....	11.53	6.75	2.07	+2.71	11.50	6.99	2.17	+2.54	11.30	7.26	2.78	+1.26
Sulphur.....	1.31	0.86	0.30	+0.13	1.94	1.02	0.33	+0.59	1.84	0.95	0.29	+0.60
Phosphorus..	3.49	2.98		+0.51	3.36	3.09		+0.27	3.91	3.55		+0.36
Chlorin.....	4.00	4.09		+0.51	6.00	5.06		+0.94	5.08	3.44		+1.59
Calcium.....	1.37	0.39	1.80	-0.82	3.60	0.73	2.24	+0.63	1.83	0.21	0.81	+0.31
Magnesium...	0.42	0.19	0.11	+0.12	1.56	0.67	0.32	+0.57	0.67	0.14	0.07	+0.46

TABLE 4.—CALCIUM AND MAGNESIUM METABOLISM (ALTER)

Day	Intake	Urine	Feces	Balance	Intake	Urine	Feces	Balance
1.....	1.35	0.37	1.73	-0.75	0.35	0.14	0.09	+0.12
2.....	1.40	0.43	1.94	-0.97	0.47	0.21	0.12	+0.14
3.....	1.37	0.39	1.71	-0.72	0.45	0.21	0.14	+0.10
4.....	3.55	0.72	2.31	+0.52	1.92	1.21	0.56	+0.15
5.....	3.62	0.73	2.14	+0.75	1.35	0.42	0.21	+0.72
6.....	3.65	0.75	2.28	+0.62	1.41	0.37	0.20	+0.84
7.....	1.32	0.12	0.46	+0.74	0.87	0.16	0.09	+0.62
8.....	0.27	0.24	0.88	+0.15	0.62	0.10	0.05	+0.47
9.....	1.42	0.27	1.11	+0.04	0.54	0.17	0.09	+0.28

During Period 2, calcium and magnesium were added to the food.

TABLE 5.—URINARY NITROGEN PARTITION
A. HEMOPHILIA CALCIPRIVA (ALTER)

Day	Amount, c.c.	Total N, gm.	Urea N, Per Cent. of Total N.	Ammonia N, Per Cent. of Total N.	Creatinin N, Per Cent. of Total N.	Uric Acid N, Per Cent. of Total N.
1	750	10.56	82.7	4.2	3.1	2.25
2	720	9.87	83.4	4.4	3.4	1.98
3	810	11.23	82.5	3.9	2.9	2.72
4	600	10.07	82.9	3.9	3.2	2.15
5	700	10.11	82.7	4.1	3.1	2.22
6	770	10.27	83.2	4.3	3.2	2.14
7	840	9.87	83.5	3.8	3.4	2.07
8	720	10.56	81.9	4.4	3.3	2.24
9	730	10.72	82.8	4.2	3.4	2.05

B. TYPICAL HEMOPHILIA (JULIUS)

1	450	6.78	82.7	4.2	3.5	1.2
2	690	7.18	83.8	4.4	3.4	1.4
3	470	6.27	83.6	3.9	3.7	1.4
4	490	6.86	85.2	4.3	3.4	1.3
5	520	7.02	82.9	4.4	3.1	1.5
6	580	7.10	84.4	4.1	3.6	1.2
7	620
8	460
9	510	7.26	82.8	4.2	3.5	1.2

TABLE 6.—SULPHUR OUTPUT IN URINE AND FECES
A. HEMOPHILIA CALCIPRIVA (ALTER)

Day	Urine				Feces, Total S, Gm.
	Total S, Gm.	Ethereal SO ₄ , Per Cent. of Total S	Inorganic SO ₄ , Per Cent. of Total S	Neutral S Per Cent. of Total S	
1.....	0.82	12.6	72.9	14.5	0.27
2.....	0.97	14.2	70.1	15.7	0.32
3.....	0.85	13.7	72.0	14.3	0.31
4.....	0.89	12.9	69.9	17.2	0.38
5.....	1.02	12.4	75.0	12.6	0.29
6.....	1.15	12.2	74.7	13.1	0.33
7.....	0.27
8.....	0.28
9.....	0.95	13.4	71.1	15.5	0.31
Average.....	0.95	13.0	72.2	14.7	0.31

B. TYPICAL HEMOPHILIA (JULIUS)

1.....	0.87	14.3	68.1	17.6
2.....	0.92	14.5	69.2	16.3
3.....	1.05	16.2	65.7	18.1	0.87
4.....	0.97	12.9	67.9	19.2	0.98
5.....	0.86	16.1	68.4	15.5	0.85
6.....	0.89	14.4	68.0	17.6	1.04
7.....	0.87	14.7	69.0	16.3	0.95
8.....	0.91	13.8	70.6	18.6	0.90
9.....	0.94	13.2	69.2	17.6	1.02
Average.....	0.93	14.3	68.3	17.3	0.94

TABLE 7.—NITROGEN METABOLISM—NORMAL BOY—5 YEARS OLD
(AFTER SCHWARZ)³

Nitrogen in food.....	9.567 gm.
Nitrogen in urine.....	7.485 gm.
Nitrogen in feces.....	0.096 gm.
Retention	14.5 per cent.
Absorption	92.7 per cent.

3. Schwarz, H.: Jahrb. f. Kinderh., 1910, lxxii, 549.

TABLE 8.—SULPHUR METABOLISM—NORMAL BOY—5 YEARS OLD
(AFTER SCHWARZ)³

Total sulphur in food.....	0.968 gm.
Sulphur in urine.....	0.592 gm.
Sulphur in feces.....	0.075 gm.
Retention	31.1 per cent.
Absorption	92.2 per cent.

TABLE 9.—(McCrudden and Fales.)⁴ NORMAL BOY, W. McC.
Weight at beginning of experiment, 27 kg.; weight at end, 27.2 kg.

URINE						
Day		Nitrogen	Sulphur	Oxid	Magnesium Oxid	Phosphorus Pentoxid
1.....		10.43	0.729	0.374	0.153	2.34
2.....		10.65	0.744	0.406	0.139	2.22
3.....		10.35	0.717	0.373	0.154	2.23
4.....		11.07	0.832	0.348	0.152	2.06
5.....		11.35	0.806	0.332	0.157	2.58
6.....		11.12	0.810	0.390	0.154	2.68
Total.....		64.97	4.640	2.223	0.909	14.11
FECES						
	Dry Feces					
1.....	2.28	1.232	0.133	1.518	0.267	0.686
2.....	19.0	0.997	0.065	1.846	0.263	0.718
3.....	20.9	1.165	0.115	1.784	0.288	0.768
4.....	23.5	1.173	0.113	2.064	0.301	0.839
5.....	15.3	0.811	0.063	1.318	0.220	0.526
6.....	21.1	1.110	0.073	1.643	0.279	0.856
Total...	122.6	6.488	0.562	10.193	1.618	4.393
Total excretion.....		71.46	5.222	12.42	2.53	18.50
Total in food.....		86.10	6.138	14.968	3.263	24.709
Retention.....		14.64	0.916	2.57	0.73	6.20
Per cent. retained.....		17.0	14.9	17.1	22.4	25.0

4. McCrudden, F. H., and Fales, H. L.: Jour. Exper. Med., 1912, xv, 453.

The protein metabolism as measured by the nitrogen and sulphur output, in the case of the two hemophilic children, is similar to the nitrogen and sulphur metabolism in the 5-year-old boy studied by Schwartz. The absorption, retention and excretion are about the same, and the partition of the nitrogen and the sulphur into the various fractions gave normal average results.

The results of the study of the mineral metabolism should be compared with the records of the study by McCrudden and Fales⁴ of the metabolism of a boy weighing 27.3 kg.

Compared with the normal boy, the excretion of calcium in the urine as compared with the excretion of calcium in the feces was about the same in both the hemophilic patients. In the case of Alter—the case of hemophilia calcipriva—there was a negative calcium balance in the fore-period, a positive calcium balance in the line-feeding period, and a decreasingly positive calcium balance in the after-period. The mineral metabolism in the true hemophilic, Julius, appears normal.

From these observations it would appear that not all hemophilia patients present similar pathologic-chemical disturbances. There seems to be no derangement in the metabolism as measured by the intake and output of nitrogen, sulphur, calcium, etc., in the case of hemophilia vera. There are, however, certain bleeders in whom the disturbing factor seems to be a lack of calcium content of the blood, and an inability on the part of their organisms to assimilate properly the lime from the food. In these cases the remedy indicated would be to administer the lacking mineral constituent in the form of the chlorid or the lactate of calcium.⁵

5. In addition to the previous numbered references, the following may be consulted:

Pratt, J. H.: Osler and McCrae, *Modern Medicine*, 1915, iv, 717.

Bulloch and Fildes: *Treasury of Human Inheritance*, London, 1911, xiva, 169.

CARMIN TEST FOR THE DURATION OF THE COMPLETE FOOD PASSAGE IN INFANTS AND CHILDREN

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During the last half century many new methods of investigation have been employed in gastro-intestinal diagnosis. A variety of test meals has been devised to determine the digestibility of foods.

Carmin, because it stains the ingesta red, and charcoal, which passes the alimentary canal unchanged, have been used to mark off stools from one diet to another. Bismuth or barium is used in roentgenography to enable us to watch the actual progress of a test meal, and as a result, various lesions of the digestive tract have been diagnosed.

However, owing to their tender age, young children cannot profit by these advances in the same degree as adults. This fact, in all probability, explains why the diagnosis of gastro-intestinal diseases in childhood is less far advanced than in adults.

The use of carmin in gastro-intestinal diagnosis dates back to the early seventies, but it is only quite recently that systematic reports of work done in this field have been published. The first to make such reports have been French pediatricists, to wit, Triboulet,¹ and Nobécourt and Merklen,² respectively.

These men have been closely followed, and without knowledge of their work, by Spivak,³ an American.

Triboulet used the carmin test on fifty children, but few of whom were less than 2 months old. Some infants were healthy, while others had gastro-enteric disorders. Carmin was given in solution. The author seems to have been interested chiefly in the duration of the total food passage. In healthy children, breast or bottle fed, at least sixteen hours were required for total elimination, and the limits ranged from sixteen to twenty-two hours. The author is not so much interested in the first appearance of carmin in the stools, and only states that the briefest interval noted in healthy children was ten hours. His chief contention is that a complete passage of less than fourteen hours is abnormal. In children with accidental catarrh, the passage time varied

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1. Triboulet: Bull. Soc. de pediat., Paris, 1909, xi, 512; 1910, xii, 85.
 2. Nobécourt and Merklen: Bull. Soc. de pediat., Paris, 1910, xii, 4.
 3. Spivak: Denver Med. Times, 1910, xxx, 171.

from nine to twelve hours, and in hyperemic and ulcerated forms from three to eight hours. The main point deduced is that (since the more severe the condition the higher up the lesion) these quick passages have a certain diagnostic value.

Nobécourt and Merklen in taking up the subject tested only healthy infants under 3 months of age (five under 1 month). Ten observations were made on six children. The first carmin colored stools came away at all periods from three to twenty-one hours, the average being ten hours. In seven observations the interval was from three to ten hours. The last colored stools came away in from eleven to thirty-eight hours—average twenty hours. The complete passage time in eight observations was not over twenty-one hours.

The chief difference between the two sets of observations refers to the first appearance of the carmin in healthy children. It was much earlier in Nobécourt and Merklen's cases, but the children were considerably younger.

Spivak applied the test to nineteen children, the ages of whom were from 4 days to 3 months. The first appearance of carmin was from three to ten hours, agreeing exactly with the figures of Nobécourt and Merklen. The maximum passage time was twenty-one hours, again agreeing with the latter figures.

Spivak also states that since in adults the feces in the colon represent the accumulation of the previous forty-eight to thirty-eight hours, i. e., of the three meals eaten on the second day before defecation, the feces must travel at a much slower rate than carmin, which may appear in the stools of healthy subjects five hours after it is swallowed, this being the shortest interval found by him in examining a large number of adults. Hence the carmin must diffuse itself directly to the colon and stain feces already present therein. This must to a certain extent be true of children.

Recently I have tested the time of the food passage on two separate sets of subjects. The first (Table 1) comprises twenty-one very young and healthy breast fed nurslings from 1 to 6 days old, at the Jewish Maternity Hospital. Carmin was given in powder form in $\frac{1}{2}$ grain doses. These babies were nursed every three hours (two with sub-normal temperature, nursed every two hours, took very little milk). The temperature varied from 96 to 99 F. The number of stools daily was two or three. The time of the appearance of red stools varied from four hours to eighteen hours, and for the disappearance of the stain from four to twenty hours were required. While my material was all newly born children, these figures do not differ radically from those of Nobécourt and Merklen and Spivak.

TABLE 1.—FROM THE CHILDREN'S SERVICE AT THE JEWISH MATERNITY HOSPITAL

Name	Sex†	Age of Child		Breast-fed How Often	Appearance of Red Stools*	
		Days	Hrs.	Hrs.	Hrs.	Mins.
S.	♂	4	22	8	9	10
W.	♂	8	11	2	9	10
G. L.	♂	8	18	8	7	
Wein.	♂	6	2½	8	12	20
B.	♂	6	2½	8	12	
V.	♀	2	6	2 and 3	4	30
W.	♀	2	6	8	6	30
F.	♀	1	3	8	18	
Vig.	♀	1	2	8	12	
Alt.	♀	4	8	2	7	30
S.	♀	4	12	8	8	30
B. A.	♀	8	2	8	9	
G.	♂	2	4	8	7	
D.	♂	1	10	8	10	
L.	♂	2	5	8	10½	
C.	♀	4	1	8	8	
B.	♀	8	2	2	9½	
K.	♀	2	6	8	7½	
Ba.	♂	3		8	9½	
Th.	♂	8	6	8	8½	
Oel.	♀	2	5	8	7	

* The stain of the stools persisted from four to twenty hours.

† ♂ means male; ♀ means female.

My second material came (Table 2) from the Beth Israel Hospital—twenty-five cases of sick children, the ages varying from 6 weeks to 6 years. The dose of carmin given was from 1 to 2 grains. The children in the great majority of cases had subfebrile temperatures (under 101 F.) and a number had been attacked with severe maladies like bronchopneumonia, endocarditis, etc. The shortest first appearance was five and a half hours, the longest fifty-two hours.

The average first time for the appearance of the carmin was from twenty-five to thirty hours. The passage time was not recorded.

In summing up we may quote also some old figures in regard to carmin passage cited by Triboulet, without names or references.

HEALTHY CHILDREN

Anonymous (Triboulet) First appearance of carmin in healthy infants, average..... 3 hrs. 50 min.
 Nobécourt and Merklen (7 in 10 cases)..... from 3 to 10 hrs.
 Spivak from 3 to 10 hrs.
 Hymanson from 4 to 18 hrs.

These figures show some congruence. Triboulet saw no carmin before ten hours.

DURATION OF ENTIRE PASSAGE

Anonymous, average 9 hrs.
 Triboulet 16 to 20 hrs.
 Nobécourt and Merklen..... Under 21 hrs.
 Spivak Not over 21 hrs.
 Hymanson 4 to 20 hrs.
 (average 12 hrs.)

These figures show considerable agreement.

TABLE 2.—FROM THE CHILDREN'S SERVICE AT THE BETH ISRAEL HOSPITAL

Name	Age	Diagnosis	Temperature, F.	Food	Appearance of Red Stools, Hrs.
S. Tr.	1 1/12	Pneumonia.....	100	Breast milk and barley water	22
S. B.	1½	Bronchopneumonia; convalescing	Normal	8
H. P.	1½	Empyema.....	100 to 102	Third diet.....	28½
T. L.	1½	Pneumonia; convalescing	Normal	Toast, cereals and milk	31
A. M.	2	Chronic empyema.....	Normal	Soft diet.....	5½
S. K.	4	Lobar pneumonia; convalescent; constipation	Normal	Third diet.....	52
M. S.	5	Rheumatic endocarditis...	100.5	Cereals, toast, eggs, milk and fruit	18½
F. W.	6	Endocarditis.....	100	Cereals, toast, eggs, milk and fruit	24½
R. A.	6	Empyema.....	99 to 102.5	Soft diet.....	28½
E. B.	4½	Chronic empyema; constipation	Normal	Soft diet.....	40½
S. Kr.	1½	Lobar pneumonia.....	100	Thirde, toast and cereals, also orange juice	28
M. M.	2	Intestinal intoxication....	100	Milk ½; barley water ¼; lactose 8%	31
B. C.	½	Bronchopneumonia.....	100	Breast milk and some barley water	12½
F. Z.	½	Spasmophilia.....	Normal	Milk ½; barley water ¼; sugar 8%	20¼
J. B.	7/12	Furunculosis.....	Normal	Milk ½; barley water ¼; lactose 8%; Mellin's food	11
I. W.	6*	Normal baby.....	Normal	Breast fed; also milk and barley water; sugar 2%	7
M. G.	½	Lobar pneumonia.....	100 to 101	Breast milk and barley water and lactose 3%	45
J. L.	9½†	Enteritis.....	100.5	Elweissmilch and barley water; also 2% of lactose	36
J. M.	½	Convalescing from bronchopneumonia	100	Breast fed.....	10
B. D.	8½†	Convalescing from ear trouble	Normal	Breast fed; milk ½, barley water ¼	8
I. G.	5½†	Diarrhea.....	100.5	Elweissmilch.....	12
B. G.	29†	Pneumonia.....	100	Breast fed.....	28
S. R.	½	Gastro-enteritis.....	97 to 101	Equal parts of milk and barley water; sugar 3%	21
R. L.	11/12	Bronchitis.....	101	Milk ½; barley water ¼; sugar 4%	11
M. T.	½	Abcess of scrotum.....	100	Breast fed, also equal parts of milk and barley water	13

* Weeks; † Months; ‡ Days.

SICK CHILDREN

The marked differences between the small figures of Triboulet (three to twelve hours) for complete passage, and the large figures of the author (average twenty-five to thirty hours), seem to be wholly due to the fact that Triboulet's sick infants all had diarrhea or enteritis, while in the author's material, bowel troubles were in a minority.

In closing we may call attention to the suggestion of Nobécourt and Merklen that the carmin test should prove of value in benign stenosis of the pylorus. If carmin given by the mouth does not appear in the stools within a definite interval, there might be good reason to suspect the existence of pyloric obstruction. In seven of ten observations the longest deferred first appearance was ten hours after ingestion, although in the three others, this was prolonged up to twenty-one hours.

We may also mention Dr. Seymour Basch's⁴ conclusions in a recently published paper on the use of the carmin test in adults. He speaks of it as a simple, harmless, reliable and convenient method for the demarkation of stools; for the estimation of gastro-enteric motility and patency; for the detection of fistulous communications of the alimentary canal with the exterior or other hollow organs; for the location of the distal end of a duodenal tube and to aid in the differentiation between esophageal diverticulum and dilatation.

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4. Basch, S.: *Jour. Am. Med. Assn.*, 1913. lxi, 1295.

PROGRESS IN PEDIATRICS

RESUME OF WORK ON TUBERCULOSIS IN CHILDREN FOR 1915 *

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CHICAGO

MODES OF INFECTION

1. Park, W. H.: The Transmission of Tuberculosis in Childhood, *Arch. Pediat.*, 1915, xxxii, 485.
2. Grulee, C. G., and Harms, F.: Tuberculosis as a Disease of the New-Born, *AM. JOUR. DIS. CHILD.*, 1915, ix, 322.
3. Péhu, M., and Chaliér, J.: A New Contribution to the Study of Congenital Tuberculosis, *Arch. de méd. des enf.*, 1914, xvii, 721.
4. Péhu, M., and Chaliér, J.: Heredity in Tuberculosis, *Arch. de méd. des enf.*, 1915, xviii, 1.
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7. Frisch, A.: Pathogenesis of Tuberculosis in Childhood, *Prag. med. Wehnschr.*, 1915, xi, 201.
8. Bartlett, F. H.: The Pathology of Tuberculosis in Childhood, *Arch. Pediat.*, 1915, xxxii, 536.
9. Senour, O. E.: Childhood Infection, Adult Death, *Kentucky Med. Jour.*, 1915, xiii, 101.
10. Hamburger, F.: Tuberculous Infection and Reinfection, *Med. Klin.*, 1915, xi, 34.

W. H. Park,¹ discussing the transmission of tuberculosis in childhood, says that intrauterine infection occurs occasionally but accounts for a very small proportion of the tuberculosis of childhood. In most of these cases the mother has had extensive miliary tuberculosis. There seems no evidence that intrauterine infection ever proceeds from the father. After birth the human infant is endangered not only by bacilli from human sources, but from diseased cattle. Cows contaminate the milk extensively, only when they have disease of the udder. One or two cows with seriously diseased udders are capable of dangerously infecting the mixed milk of a whole herd. It is fairly certain, however, that when tubercle bacilli contained in milk are heated to 140 F. and held at that temperature for twenty minutes they are destroyed. Butter is known to contain tubercle bacilli when made from milk infected with them. The evidence that butter actually transmits tuberculosis is less direct than that milk does. This is partly because the bacilli are fewer,

* Submitted for publication Jan. 10, 1916.

and because butter is not usually taken at an age when tuberculosis of the bovine type is most likely to be transmitted.

Although recent investigations have definitely proved that bovine bacilli infect infants and to some extent older children, yet the evidence is equally clear that most infections are transmitted by one human being to another. In the case of infants and young children, the greatest danger lies in being attended by a tuberculous mother or nurse. This direct human contamination can be avoided only by keeping the child from contact with tuberculous persons.

C. G. Grulee and F. Harms² call attention to the subject of tuberculosis in the new-born, with the hope not of adding a great deal to the literature, but of stimulating interest in the subject, which has been so long neglected.

Their case is as follows: The child was born of a mother with a supposedly healed tuberculosis, and with only one subjective symptom, a severe leukorrhea of unknown cause. The mother survived the child many months. The baby fifteen hours after birth developed a high temperature, which continued until his death on the eleventh day. There was a distinct tendency to regurgitation of food. Generalized convulsions developed on the seventh day and continued up to twenty-four hours before death. On physical examination the child showed only an enlarged liver and spleen. At necropsy a generalized tuberculosis, affecting most markedly the abdominal organs, and especially the periportal lymph glands, liver, and spleen, was found. The tuberculosis was miliary in type but the stage of the tubercles suggested that the disease had begun in utero. Many tubercle bacilli were found in all sections of the tuberculous area.

The authors find that congenital and placental tuberculosis is being reported with increasing frequency within the last few years. From a pathologic standpoint there are two forms of tuberculosis of the new-born, both miliary in type, namely the pulmonary and the abdominal. The pulmonary form is not always of placental origin and seems much more likely to result from aspiration of the liquor amnii or vaginal secretions at the time of birth. The abdominal form may be termed the general miliary form, for, while the lesions are more marked in the abdominal cavity, the thoracic viscera are always involved.

Clinical data of tuberculosis of the new-born are so scant that no conclusions can be drawn as to the symptomatology. The writers think it not at all impossible that the early temperature in their case had nothing to do with the tuberculosis, but was simply the so-called inanition fever, frequently noted at this time. The combination of enlargement of the spleen, high, irregular temperature, and enlargement of the liver, together with tuberculosis in the mother is suggestive.

In diagnosis little can be expected from the tuberculin tests. In the newborn the tuberculin test has been negative almost without exception. The prognosis has always been fatal. The duration of life has varied from twenty-four hours to twenty-five days.

M. Péhu and J. Chaliér³ have collected from the literature sixteen undoubted cases of congenital tuberculosis, which were not included in their last paper on the subject or which since have been published. They conclude that authentic cases of congenital tuberculosis are rare, as they were able to collect only fifty-one, all told. The infection occurs during or at the end of pregnancy, when the placental circulation is established, and is the result of a bacilleemia which is usually a terminal event. They should always be regarded as examples of transplacental heredo-contagion.

M. Péhu and J. Chaliér⁴ summarize their paper on the inheritance of tuberculosis as follows: Direct transmission of tuberculosis by the sexual cells (ovule and spermatozoa) has not been demonstrated. Theoretically it is possible, but in the strict sense of the word, heredity of the germ of tuberculosis does not exist. Transplacental heredo-contagion exists, but owing to its extreme rarity this mode of propagation of tuberculosis is of little importance. The dystrophies which at times have been observed in tuberculous children are not specific in character. It has not been proved that there is a special hereditary predisposition to tuberculosis. The descendants of the tuberculous offer a receptive soil for all diseases and not for tuberculosis in particular. Nor has it been demonstrated that there exists an hereditary transmission of immunity for tuberculosis. It is in the infected environment in which they live that the children of the tuberculous become contaminated. Rational prophylaxis will protect them from the disease.

A. Ghon and B. Roman add another contribution to the pathologic anatomy of tuberculosis in childhood, touching the matter of the propagation of the tuberculous process from the primary pulmonary lesion to other tuberculous processes in the body. They first quote a case of Ganghofer's and show how it confirms Ghon's previously reported theory of a primary pulmonary lesion and helps toward the solution of the new phase of the question. This case was one of acute tuberculous meningitis of the base of the brain, with a few acute miliary tubercles in the spleen, lungs, and liver and older tuberculous lesions in the lungs and their lymphatics. A small, date-like, caseous area in the right lung was evidently the primary lesion, as this lesion and those in the draining lymphatics were the most advanced and as there could be no other explanation of the acute miliary tuberculosis of brain, liver, and spleen than rupture into the blood stream.

Ghon and Roman report six cases, all confirming Ghon's early theory of a primary pulmonary lesion and all showing that extension

of the tuberculous process takes place through the lymphatics draining this area. In five of the cases the primary lesion was on the lateral part of the interlobular surface of the right upper lobe. The lymphatics of this area pass through the bronchopulmonary lymph nodes to the lymph nodes in angles of division of the bronchi, thence to the nodes on the anterior surface of the right pulmonary hilus. The difference in the changes in the interlobulary nodes between the upper and middle lobes and those between the middle and lower lobes proved this point, as did also the difference between the upper and lower tracheobronchial glands. Of not less significance was the difference in size of the anterior bronchopulmonary glands at the hilus and the posterior ones. The greatest changes were always in the glands situated in direct topologic relation to the involved pulmonary area.

As regards the course of the tuberculous process, the authors divide the six cases into two groups. In Group 1, including three cases, there was no tendency to heal. The tuberculous process was a progressive one. The fact that the tuberculous process can remain for a time limited to the portal of entry and its outgoing lymphatics, is important in considering tuberculosis in childhood.

Group 2 also included three cases and there was a tendency in some of these lesions to heal, but they all showed progressive lesions as well. The question of the relation between the progressive lesions and those with a tendency to heal is interesting. Was the progressive lesion an exogenous new infection or an endogenous recrudescence? Hamburger has pointed to the importance of this question from a clinical standpoint and from the anatomical one it is not easy to answer, nor is it easy to determine which lesion is primary, where two or three pulmonary lesions exist. It is doubtless true that two pulmonary lesions may be due to distinct exogenous pulmonary infections or one may be primary and the other secondary from aspiration from the primary lesion. The authors think that these questions can not now be definitely answered and that progress will be made only when exact anatomic examinations are made, with these questions kept clearly in mind.

A. Frisch⁷ reports the necropsy findings which fulfill the theory of Ghon and Roman in regard to the spread of the disease, in a case of extensive tuberculosis in an 8 weeks-old baby. The oldest lesions were three cheesy pneumonic areas in the left lung, two of which were probably the result of a lymphogenous infection from the first. From these areas the disease had spread to the left tracheobronchial glands, then evidently to the right tracheobronchial glands, as caseation was less advanced in this than in the first group. In the mucous membrane of the left bronchus were tuberculous changes which were the

result of contact infection from the pulmonary lesion. In the middle ear were lesions of hematogenous origin, as were also in the mucous membrane of tonsil, adenoid tissue, tongue and epiglottis. These may, however, have been due to contact infection from sputum. In direct relation to the lesions in the nose and throat, were the tuberculous changes in the submental, submaxillary, retropharyngeal and cervical glands.

The tuberculous changes in the stomach and the small and large intestines were more recent than those elsewhere in the body, and consisted of miliary tubercles. They were either of hematogenous origin or due to contact infection from sputum which had been swallowed. Changes in the mesenteric glands were the direct result of the intestinal infection.

In the spleen, liver, pancreas and adrenals were miliary tubercles of hematogenous origin. Besides the three primary lesions in the lung, there were many miliary tubercles also of hematogenous origin.

F. H. Bartlett⁸ analyzed 178 necropsies, in which tuberculosis was found. He concluded that in children the primary infection of the lung was the usual mode of infection, since 82 per cent. of the cases were of the pulmonary type. The absence of tuberculous lesions in the lungs in fourteen cases, and the presence of such lesions in the bronchial lymph nodes in seven of these, seemed to show that it was possible for the tubercle bacilli to pass through the lungs without localizing there. The largest number of cases were of inhalation origin, as shown by the large percentage of cases in which the pulmonary lesions were the most advanced in the body.

The marked tendency to rapid and general dissemination of tuberculous lesions in infants was well shown. In view of this fact the survival of any young infant infected with tuberculosis for more than six months after infection was very remote, while healing in young infants was practically out of the question. In the entire series, not a single healed tuberculous lesion was found, and attempts at healing, as shown by calcified areas, were observed in only five instances in the lungs and thirteen in the lymph nodes. Only twice was it found in infants less than a year old, and in both instances, the extensive generalization of the tubercles throughout the body gave evidence that the small calcareous areas present did not prevent the spread of the infection.

The comparative frequency of tuberculous meningitis in young infants was noteworthy as evidence of the very great general dissemination of tuberculous lesions in young subjects. There was a smaller proportion of cases of tuberculous meningitis among children who acquired the disease by ingestion than among those who acquired

it by inhalation, which finding was in keeping with the fact that the cases infected through ingestion showed rather less tendency to generalization than did the respiratory cases.

F. Hamburger¹⁰ differentiates primary infection in tuberculosis from reinfection. Primary infection usually takes place from a sufferer of phthisis who has tubercle bacilli in the sputum. The person infected is usually a child. This is proved by the following facts: Children who live with tuberculous individuals almost without exception react to tuberculin and, when children less than 2 years old become ill with tuberculosis, they have associated with some one with tubercle bacilli in the sputum. The opinion that infection can be carried from cattle to man is not positively proved. It seems inconceivable that infection can be carried in this way and there are no reports in the literature of instances of direct infection of infants from cattle with tuberculosis of the udders.

Primary tuberculous infection usually takes place by inhalation. This statement is founded on the law of primary lesion and regional lymphatic gland involvement, as well as animal experimentation. Animal experiments show that infection with tubercle bacilli simultaneously causes lesions at the point of inoculation and in the lymphatic glands draining the infected area. Moreover, when the disease has become advanced, the changes in the glands are more widespread and severe than at the point of inoculation.

Primary infection takes place easily. Association for a short time with an individual who coughs is sufficient to produce infection. Hamburger quotes an instance of a child being in a room with a consumptive only half an hour and dying a few weeks later of tuberculosis. Primary tuberculous infections during the first year are very serious, but the seriousness decreases from year to year, so that primary infection after the sixth year is without danger.

Reinfection with tuberculosis is either endogenous or exogenous. Endogenous infection may be bronchogenous, hematogenous, or lymphogenous. Bronchogenous infection results from mucus being carried from the primary lesion to other portions of the lung during a spell of coughing. The mucous membranes of the larynx or nasopharynx may also become infected in this way.

Hematogenous and lymphogenous infection results from rupture of the primary lesion into the blood or lymph vessels.

When tubercle bacilli penetrate the tissues of an individual already infected, there is a reaction between the specific antibodies and the tubercle bacilli (an allergic reaction). If the reaction is energetic, all or most of the bacilli are killed, so that no lesion develops immediately, but after months or years of quiescence an exacerbation may occur. Often in this case lesions in the glands draining the area of

reinfection become active before the area of reinfection itself. Very frequently, however, no exacerbation ever occurs, something which shows that immunity to reinfection does exist.

Exogenous reinfection is almost without exception an inhalation infection. It occurs very frequently, especially in individuals who are associated with patients with phthisis. Many persons develop an immunity to exogenous reinfection, while for many it is very dangerous.

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The experience of E. Rumpf and J. Zeissler¹¹ has shown that there is a great difference in the results of finding tubercle bacilli in the blood by microscopic examination and by animal experimentation. In nearly every case examined they found bacilli microscopically, while only 8.5 per cent. of the animals inoculated developed tuberculosis. The conclusion is that the bacilli found microscopically in the blood were not virulent tubercle bacilli, especially as, in spite of all care, they could not grow on artificial mediums. It is held, however, that occasionally careful examination will reveal tubercle bacilli in the blood of tuberculous individuals.

A. Jousset¹² calls attention to the fact that when a guinea-pig is inoculated with tubercle bacilli, a bacillemia develops before a lesion. He suggests that a similar bacillemia occurs in the human, and, in fact, finding after death, the tubercle bacilli in the heart's blood of a number of infants, he has been able to prove that such a bacillemia does exist in infants. That the tubercle bacillus does not live a saprophytic existence excludes a cadaveric contamination with this organism.

Jousset's observations were made on six infants from 5 to 10 weeks old and on two from 6 to 7 months. Clinically they presented the ordinary picture of an athrepsia with gastro-intestinal disturbances. The cutaneous reaction was usually negative. Jousset says that in a breast-fed baby a regular decline in weight with a persisting diarrhea, which cannot be explained, suggests a tuberculous bacillemia, and he believes a large part of infant mortality attributable to this condition.

A. Philip Mitchell,¹³ continuing his studies begun in 1911, investigated the relative frequency of the human and bovine type of tubercle bacillus in lymph glands, obtained at operations and at necropsies, on children.

The investigation consisted of gross examination of the glands, inoculation of guinea-pigs with emulsion of glands, and microscopic examination of glands.

The glands of twenty-nine children below 12 years were obtained at necropsy, but cultures of tubercle bacilli grew only in twelve instances; eight were the human type of bacillus and four the bovine. In the four instances of infection with the bovine type there was a more extended caseation of the mesenteric glands than of any other group.

The bronchial and mesenteric glands of eighteen children showing no evidence of tuberculosis at necropsy were inoculated into guinea-pigs. Tubercle bacilli were demonstrated in but a single instance in the bronchial glands of a child aged 4. The bacilli were of the human type.

The glands of eighty children were obtained at operation. Forty-two of the children resided in Edinburgh, thirty-eight in the neighboring country. In seventy-one, or 88 per cent., the bacillus isolated was of the bovine type; in nine, or 12 per cent., of the human type. Most of the children were under 2 years of age, and 84 per cent. had been fed unsterilized milk since birth. In the majority of instances, except for the glandular enlargement, the children were in robust health and gave no other clinical evidence of tuberculosis. The influence of the acute infectious diseases, as apparently favoring the dissemination of the disease in the glands, was noted in fifteen cases. In not a single case was there a history of pulmonary tuberculosis in other members of the family.

In conjunction with this study, Mitchell¹⁴ investigated the prevalence of tubercle bacilli in the milk supply of Edinburgh. Of 406 samples of mixed milk, eighty-two, or 20 per cent., contained tubercle bacilli.

Mitchell draws the following deductions from his work: The results of inoculation with necropsy material, because the cases were few, cannot be considered conclusively as to the frequency of bovine and human types of infection, but they furnish evidence that in fatal tuberculosis in children the human bacillus is the main contributor to the mortality rate. Having demonstrated that a considerable proportion of the tuberculosis affecting children in Edinburgh is of bovine origin, and that the milk supply of this city is frequently infected with tubercle bacilli, and having demonstrated that a certain number of deaths occur from this bacillus, he no longer regards bovine bacilli as a negligible factor in the spread of tuberculosis among children.

Mitchell hopes that the high degree of tuberculosis contamination which he has found in the Edinburgh milk supply may be an effective argument for those who are working with the legislature in the cause of pure milk.

H. L. Coit¹⁵ is of the opinion that it has not yet been determined to just what extent bovine tuberculosis is dangerous to human beings. The introduction of tuberculous infection into a herd of cows sometimes occurred when new stock were purchased. It seemed that dealers sometimes "plugged" their cattle with tuberclin before selling them, so that they did not react to the tuberculin test. To avoid danger from this source, it should be made compulsory to brand every animal that reacted to the test. It is also desirable that owners of dairy farms should breed their own cattle for replenishing their stock. The government spent many thousands of dollars each year making tuberculin tests for private individuals and yet refused to cooperate with the Milk Commission, entirely failing to appreciate that by cooperation far better results could be obtained at a much reduced expenditure.

Coit reviewed the investigations made in New York City, by Dr. Hess, and, in England, by Dr. Anderson, with reference to the incidence of bovine tuberculosis among children using ordinary uncertified milk. The results of their investigations seem to show that the danger of infection with the bovine bacillus was very slight, though all agreed it did occur. The writer urged members of the Milk Commission and other organizations interested in a pure milk supply, to take more interest in the work and recommended that, for the purpose of making the tuberculin tests, only veterinarians having the standing of a professor in a veterinary college be employed.

F. M. Pottenger¹⁶ thinks that it has been fairly demonstrated to the satisfaction of the scientific world that: 1. Bovine infection can be transmitted to human beings. 2. While bovine infection is accountable for about 10 per cent. of tuberculosis, human infection is accountable for most cases in the human race. 3. While bovine infection is common, it is rarely found in adults.

In regard to this difference in frequency of bovine tuberculosis in children and adults, Pottenger says we must believe either that bovine infection for the most part becomes nonvirulent or heals, confining its sphere of activity to the child, or that the bovine bacillus changes its type by residence in the human body. What seems most probable to the writer is that the bovine bacilli, after living in human tissue for a time, adapt themselves to the new conditions, and gradually become the bacilli which would naturally be produced in human soil.

A. de Besche¹⁷ reports an instance of infection with both the human and bovine type of tubercle bacilli. He says it is well known that there

has existed a marked difference of opinions as to how atypical strains of tubercle bacilli isolated from cases of tuberculosis are to be regarded. A number of investigators have declared that the strains revealing atypical characteristics are transitional forms between the human and bovine types.

It has been stated by the English Tuberculosis Commission in their final report that strains which appear as transitional forms cannot be so regarded, because a closer study of cultures may show that the bovine and human tubercle are mixed.

In the writer's case the culture was isolated from a mesenteric gland of an 8 months-old child, who had died of general tuberculosis. On isolation in the usual way, the bacilli showed the cultural peculiarities characteristic of tubercle bacilli of the human type. Testing the virulence, however, indicated a virulence for animals not corresponding to the human type. Further experiments proved the presence of both the human and the bovine type of tubercle bacilli.

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According to T. Frazer,¹⁸ our ideas as to the frequency and significance of the v. Pirquet tuberculin test have suffered change. Recent experiments seem to indicate that the test may be not only of diagnostic value, but also preventive.

A positive cutaneous reaction is less frequent in children than it was once thought to be. The former high percentage of positive reactions was due to the fact that the test was applied to infected children of the poorer classes. Also a difference in technic may play a part in the variation of the number of positive reactions. While there is an increasing percentage of reactions with years, the view held that the reaction has significance only during the first two years of life, is not borne out by recent figures, and all reactions occurring up to the age of 10 years should be regarded as suspicious.

With the recognition of this increasing infection and also of the relation which exists between infection in childhood and clinical tuberculosis in later years, it follows that, if the infection is detected and treated, a great stride forward will be made in the prevention of clinical tuberculosis. The applicability of the test, then, is to detect the presence of infection at the earliest possible moment, and to this end its employment annually would contribute in no small degree.

B. S. Veeder and M. R. Johnston¹⁹ conjectured from their work at the St. Louis Children's Hospital that positive tuberculin reactions were much less frequent than was generally supposed. To discover whether this was a misapprehension or a fact they went over the clinical records of the past three years, tabulated the results of the tuberculin tests, and summarized as follows: A study of tuberculin tests in 1,321 hospital children in St. Louis shows that the percentage of positive reactions reaches a maximum of 44 per cent. between the years of 10 and 14. (Cases of clinical tuberculosis are included.) Where clinical tuberculosis was excluded, the percentage for this age period is only 36 per cent. These figures are much lower than the usual 90 per cent. figure, which has gained such widespread publicity and which is based on the figures of Hamburger of Vienna.

The extent of infection among children varies in different cities and countries and is dependent on such factors as living and social

conditions, the amount of tuberculosis in the community, and the exposure of the child to open tuberculosis. In all probability the extent of infection also varies among different classes of society in the same community. No conclusions as to the extent of infection with the tubercle bacilli can be drawn from statistics of one city or class and the statement that 90 per cent. of individuals are infected by puberty is an extreme exaggeration of the actual condition.

W. R. Ramsey²⁰ gives his results of v. Pirquet reactions made with old tuberculin and bovine tuberculin on children in the State Hospital for Crippled and Deformed Children in St. Paul. In all 116 children were examined, fifty-eight boys and fifty-eight girls. Whenever a positive reaction was present for one tuberculin, it was present for the other also.

Of the fifty-eight boys, twenty reacted positively and thirty-eight negatively. Of the fifty-eight girls, twenty-two reacted positively and thirty-six negatively—a total of forty-two positive and seventy-four negative reactions.

Seventeen boys and eleven girls gave a negative v. Pirquet, when the clinical diagnosis was tuberculosis of the bone. Of the total number of fifty-eight diagnosed clinically as tuberculosis, only twenty-eight gave positive v. Pirquet reactions.

M. S. Voronin²¹ tested 140 infants for the v. Pirquet tuberculin reaction, with undiluted tuberculin and with dilutions of 5, 10, 15, 25, 50, and 75 per cent. One hundred and thirty of the infants were between 2 days and 4 months of age; ten were between 6 months and 1 year. Of the 140 tested there were only two positive reactions and those were but weakly positive, one with undiluted tuberculin and one with a solution of 75 per cent.

M. N. Keifetz²² examined 276 children of various ages for the v. Pirquet reaction to tuberculin and found it positive in 53 per cent. The children who lived in favorable surroundings gave a positive reaction only half as often as children living in poor and unhygienic surroundings. The v. Pirquet test is specific for tuberculosis and indicates a tuberculous infection. Keifetz thinks it desirable to examine all school children by this simple and decisive method.

G. Salvetti²³ vaccinated 630 children by the v. Pirquet method; 166 gave a positive, 327 a negative and 37 a doubtful result. Children who showed clinical evidence of tuberculosis gave negative reactions in 18 and doubtful reactions in 8 per cent. of the cases. Of twenty-one cases of tuberculous meningitis, fifteen gave positive reactions, also two cases of erythema nodosum. If the children contracted measles, the previous positive reaction became negative in a large per cent. of the cases.

J. B. Manning and H. J. Knott²⁴ performed the v. Pirquet test on 228 children, 166 of whom had been exposed to tuberculosis and sixty-two of whom had not been exposed.

Eighty-four of the 166 children, who had been or were at the time of examination still living in intimate contact with adults suffering from active tuberculosis, gave an active tuberculin test. Sixty-four, or 82 per cent. of these showed no clinical evidence of the disease; fifteen, or 17.8 per cent., had lesions in varying degrees of activity. There were seven children with bronchial gland tuberculosis, one with active keratitis, two with cervical adenitis, four with distinct lung invasion, and one with tuberculous peritonitis.

Eighty-two of the group of children who had been exposed to tuberculosis gave a negative v. Pirquet reaction.

Of the sixty-two children who had not been exposed, fourteen, or 22.5 per cent., gave positive reactions and forty-eight, or 77.4 per cent., gave negative reactions.

In the entire series of 228 cases with so many known exposures it is interesting to note that the percentage of reactions was only 42.9 per cent. These figures do not bear out Fishberg's assertion that there is but slight difference in the number of positive reactions among those who live in a tuberculous milieu and those who do not.

O. F. Rogers²⁵ inquired into the history of sixty-nine children subsequent to their discharge from the Massachusetts General Hospital, where they had given a positive v. Pirquet reaction. The history inquired into covered a period not less than one year, and not more than four years. He was able to ascertain the fate of fifty of the sixty-nine. Seventeen of these, of whom eleven, or 65 per cent., had died, were below 2 years of age; four, or 23 per cent., showed no evidence of active tuberculosis; and only three were really well. Thirty-three were over 2 years of age, and of these only seven, or 21 per cent., had died. The outlook was, then, nearly three times as favorable in the second as in the first group.

Rogers draws the following conclusions from his study: A positive cutaneous tuberculin reaction before the age of 2 seems to indicate that the child's life is likely to be short. The mortality among all children under the age of 10, who react to the v. Pirquet test, is much higher than among those who do not.

M. Fishberg²⁶ applied the tuberculin test to 588 children under 15 years of age, in whose homes there was no person known to have tuberculosis. His aim was to ascertain whether only children raised in a tuberculous environment run the risk of infection with tuberculosis, while children living under similar social, economic, hygienic and sanitary conditions, but whose parents are nontuberculous, escape infection.

Of the 588 children 310, or 52.7 per cent., gave positive reactions. The test was applied only once and the author is of the opinion that, if it had been applied a second time to those who did not react the percentage of positive reactions would have been increased 10 to 20 per cent.

Fishberg says there are several problems to be discussed in connection with these findings. It is of immense interest to know whether a positive reaction is an indication of infection with the tubercle bacillus; if so, how have these children become infected; and finally, what is the outlook for these children—are they destined to suffer from clinical tuberculosis sooner or later? All available evidence seems to show that these infections during childhood are harmless to the vast majority of persons. The fact that so many give positive reactions to tuberculin and yet are healthy is sufficient proof that infection with the tubercle bacillus is not alone enough to produce phthisis. Moreover, Fishberg thinks that these mild lesions are not only innocuous, but even beneficial, since they protect the individual from exogenous reinfection. Persons who have not undergone a mild infection during childhood, when infected with the tubercle bacillus, are likely to develop hematogenous tuberculosis of a rapidly fatal type.

Fishberg makes the following summary of his article: The cutaneous test satisfactorily shows whether a person has been infected with the tubercle bacillus or not, but it is of little value in the diagnosis of the disease known as tuberculosis in its various manifestations. In the large cities and even in the small rural communities most of the children have been infected with tuberculosis before reaching adolescence, though they have not necessarily suffered as a result of this infection.

G. H. Cattermole²⁷ performed the cutaneous tuberculin test on a number of children in Colorado, in order to ascertain, if possible, the frequency of this disease among children in that state.

Of sixty-six children tested, twenty-five, or 38 per cent., gave positive reactions; forty-one, or 62 per cent., gave negative reactions. Thirty-four of these children had tuberculous parents, while twenty-nine had parents free from tuberculosis. In spite of the fact that 50 per cent. of the children had parents who had suffered from active tuberculosis, only 38 per cent. of the children showed a positive reaction at the time of examination.

In twenty-two instances tuberculous children had tuberculous parents. In twenty-seven instances nontuberculous children had nontuberculous parents. In twelve instances nontuberculous children had tuberculous parents. In one instance a tuberculous child had nontuberculous parents.

Of the twelve children who did not react, but who had tuberculous parents, three were less than 2 years old; one was 2 years old; one

was 4 years; one 5 years; three were 6 years; one was 7 and two were 9 years old.

Cattermole draws the following conclusions from his study: Children who are infected with large numbers of tubercle bacilli, as those living in the tenements of the cities, or near active pulmonary cases, develop hypersensitiveness, as shown by the tuberculin reaction.

When children have never been infected, or in cases in which the number of bacilli received is very small and the child's resistance good, as in Colorado, they do not react and are either not infected or are immune.

Possibly all tuberculosis is contracted in childhood and from three-sevenths to six-sevenths of the population acquire immunity at this time; while the others succumb to the more acute tuberculous conditions of childhood or later show the chronic pulmonary type of adults, which is believed never to occur except in those who have been infected and rendered partially immune in childhood.

In the prevention of tuberculosis the aim should be to protect infants from all exposure, and older children from massive infection. Moderate and gradual infection in older children probably insures immunity.

W. A. B. Young²⁸ in the Manchester Children's Hospital has tried to ascertain the incidence of tuberculosis among infants suffering from malnutrition and not giving any clinical evidence of the disease. He performed the tuberculin test on 113 of them. He found a positive reaction in thirty-one, a negative in seventy-seven, and a doubtful in five. No child under 3 months gave a positive reaction, and only one under 6 months. Of fifty-five children under 1 year, seven gave positive reactions; of eighty-five under 1½ years, fifteen gave positive reactions; of ninety-three children under 2 years nineteen gave positive reactions. Thus, a considerable number of marantic children, with no clinical evidence of tuberculosis, gave a positive tuberculin reaction.

G. T. Palmer²⁹ discusses the possibility of a tuberculin reaction in the child after the drug has been administered to the mother, and cites a case in point. A woman suspected of having tuberculosis was given 1 milligram of tuberculin intradermally. The next day her six months-old, nursing baby was reported to have developed bronchitis or bronchopneumonia and a week later definite meningeal symptoms. Examination showed extensive pulmonary involvement and meningitis. The child died ten days after the test had been given to the mother.

Considering the likelihood that the child was tuberculous, as he had been cared for frequently by a father who had open pulmonary tuberculosis, and considering the infrequency of any effect on the child of the administration of tuberculin to the mother, Palmer thinks it highly probable that the relation of the test to the illness of the child

was purely one of coincidence. This view is supported by the fact that for two or three weeks before the acute illness the child had been indisposed.

The literature on the effect on the nursing child of a tuberculin test given the mother is very meager, but seems to confirm the theory of coincidence. Though there is no question of the fact that toxins as well as immune substances may be transmitted through the milk, it seems hardly probable that in this case sufficient tuberculin could have reached the child to cause the slightest disturbance.

The author finds the case interesting and suggests that possibly greater care should be exercised in giving tuberculin to the nursing mother, and that the element of coincidence should be fully considered when unfortunate complications follow its use.

J. A. Colliver³⁰ experimented to ascertain whether the skin in one part of the body is more susceptible to tuberculin than another. He tested fifty children and selected the dorsum of the hand and foot, the inside of the knee, the shoulder, the neck, the back, and the ulnar side of the forearm for the site of vaccination. Undiluted tuberculin was inoculated with the v. Pirquet drill. Measurements and observations were made every two hours after the inoculation for the first fourteen hours, then, beginning the next morning, every four hours for the next twelve hours, and then every six hours, until the reaction reached its maximum.

The conclusion drawn from the experiments was that there is no good reason for making the v. Pirquet tubercular cutaneous test elsewhere than on the forearm, and that this location has the advantage of being convenient.

D. B. Lees³¹ reports four cases of incipient tuberculosis in children and emphasizes the value of percussion properly performed, as an aid in diagnosis. He says, however, that, to arrive at a sound conclusion, it is essential to adopt a correct method. The inadequate and misleading statements of textbooks in regard to percussion in incipient tuberculosis are founded on examination of patients in sitting or standing posture. This posture invariably leads to false conclusions in the examination of the front of the chest, because it does not allow of complete relaxation of the muscles or of the counter resistance, which is necessary for even the lightest percussion stroke. It is essential for the examination of the front of the chest that the patient assume a recumbent position on a comfortable couch. For the examination of the back of the chest he should be in a sitting and slightly stooping posture, with his hands on the front of the opposite shoulders, the elbows pressed together, and the muscles relaxed. The physician should press firmly with the terminal phalanx of his left hand on the

spot to be examined, keeping all the rest of his hand and arm away from the patient's chest wall. He should then percuss lightly with the finger of his right hand and measure in finger breadths the diameter of the dull area.

In any case of phthisis it is possible to detect the existence of a typical series of dull areas, which are found in the same position in case after case. In an early stage of the disease, when the symptoms are suggestive but not conclusive, the discovery of the typical series of dull areas is sufficient to establish a diagnosis. Simple collapse of the lung, common in young children, is irregular in distribution and not arranged in the pattern characteristic of tuberculosis. Bronchopneumonia of nontuberculous origin affects mainly the lower parts of the lungs. In the early stage of pulmonary tuberculosis the entry of air is very defective over the typical dull areas and there may be no morbid sounds. This fact is likely to cause error in diagnosis. Even at a late stage, when the areas are large, there may be a few or no morbid sounds.

W. Overend²² describes the shadows seen in Roentgen-ray plates of children with tuberculosis. A diffuse shadow extending from the vertebral ends of the third rib to the sixth rib is due to enlargement of the tracheobronchial glands and may be called tracheobronchial or superior opacity. A shadow just below the level of the sixth rib, running directly into the hilum and obliterating the narrow isthmus between the hilum and the cardiac opacity, is caused by congestion of the bifurcation glands and is called the intermediate opacity.

Shadows in the interspaces are due to perivascular and peribronchial tuberculous infiltration. Sometimes these interspaces become more translucent during inspiration and the shadows in the interspaces seem to suggest a close interlacement of lymphatics or a fine pleuritic exudate.

Shadows at the hilum are due to swollen, caseous, or calcified glands and the density of the shadows increases in this order. If the hilum is broad, irregular in outline and uniformly diffuse or cloudy in appearance, the process is active.

In the pulmonary field may be seen a fine shadowy network or shadows of small tubercles or large tuberculous foci. A general mottling is a sign of phthisis but not of activity, as it may be due to a healed tuberculous lymphangitis. Morton and Owen think that mottling is due to the crossed shadows of thickened lymphatic vessels. The occurrence of small shadows the size of a pinhead, standing separately or in conglomerate groups, producing a cloud effect, is diagnostic of activity. If fibrosis takes place, the opacities are more dense and sharply defined.

J. L. Morse²⁸ discusses the subject of what constitutes tuberculosis in childhood. He emphasizes the importance of distinguishing between tuberculous infection and tuberculous disease. For all practical purposes the infant comes into the world free from tuberculosis. In round numbers 10 per cent. of all infants become infected with tuberculosis before the end of the first year of life, and at 16 years, not more than 10 per cent. have escaped infection. However, a very small percentage of these children have tuberculous disease. Those who are well and show no evidence of symptoms of tuberculous disease are little, if any, worse off than those who have not been infected. In fact, it is probable that they are better off in that they have established an immunity to tuberculosis.

A positive tuberculin test signifies in itself nothing more than tuberculous infection; it does not denote tuberculous disease. Tuberculous infection in childhood is almost invariably glandular. In the struggle to overcome the infection the glands become enlarged and indurated. When the cervical glands enlarge, they can be seen and felt. The mesentery glands can be felt if sufficiently enlarged, while the tracheobronchial glands, although neither visible nor palpable, give rise to certain definite physical signs. d'Espine's sign which, when present, is said to indicate tuberculous tracheobronchial glands, shows that there is some enlargement of these glands, but shows nothing as to the nature of the enlargement. If a positive d'Espine sign is associated with a positive v. Pirquet reaction, the chances that the enlargement is tuberculous are increased. These chances are further increased if the sign is persistent.

The significance of Roentgenographs which show a shadow in the region of the tracheobronchial glands is exactly the same as that of a positive d'Espine's sign. Great care should be taken in interpreting Roentgen-ray plates. Only the opinion of an expert is of much value, and even that is not infrequently wrong.

There is little room for difference of opinion as to the presence or absence of tuberculous disease of the cervical glands or of the bones. The greatest opportunity for opinion as to whether a child has or has not tuberculous disease, arises when a child showing a positive tuberculin reaction manifests symptoms of general constitutional disturbance, such as fever, rapid pulse, loss of weight and strength, debility, fatigue, anemia and dry cough, without any evident signs of disease. The presence of a definite history of exposure to tuberculosis is strong evidence in favor of an active tuberculous focus somewhere.

Too much attention must not be attached to a slight elevation of temperature, for this is a very common thing from minor causes. In the writer's opinion, it is much more likely to be due to infection in

the nasopharynx or the accessory sinuses, pyelitis or indigestion, than to tuberculosis.

Disturbances of nutrition, anemia, debility, fatigue and malaise are all symptoms of indigestion, overwork in school, late hours, lack of fresh air and many other things, as well as to tuberculosis. A dry cough may be due to nasopharyngeal irritation, enlargement of the lingual tonsil and various other local irritations, as well as to tuberculous tracheobronchial adenitis.

It is evident, then, that the presence of these symptoms does not justify a diagnosis of tuberculosis in the absence of physical signs of disease, even if they are associated with a positive v. Pirquet reaction and the diagnosis of tuberculosis should only be made after a careful and unprejudiced investigation and consideration of all the factors in the individual case.

J. B. Hawes³⁴ gives a number of points to be borne in mind when the diagnosis of tuberculosis in children is being considered. He says it must be remembered that there is a difference between tuberculous infection and tuberculous disease. Eighty to 90 per cent. of individuals are infected with tuberculosis before the age of 15 years, but the fact that the great majority live at least an average lifetime shows that this does not necessarily imply disease; that tuberculosis in childhood is primarily a disease of the glandular system, while in infancy it takes the form of a general septicemia; that bovine as well as human sources are of importance in considering exposure; that in childhood, by the time the lungs are involved, the disease is far advanced; that constitutional signs and symptoms are of importance. The principal ones are ease of tire, loss of weight or failure to gain weight, pallor, malnutrition and debility; that, while in adults there is no characteristic cough, in children there is a cough, which is more or less characteristic of bronchial gland enlargement; that a positive tuberculin reaction is of infinitely greater importance in children than in adults; that, though the Roentgen-ray in children may show enlarged bronchial glands it does not prove these glands to be necessarily tuberculous.

Hawes says also that the physician must not fail to realize the responsibility of stamping a child tuberculous, and that, if in doubt, he would be wise to institute proper treatment, without casting the stigma of tuberculosis on the child. Also it must be borne in mind that diseased tonsils, and increased adenoid tissue, a chronic middle ear inflammation, and other conditions may simulate tuberculosis.

E. Lackner and A. Levinson³⁵ describe the permanganate test for spinal fluid and report its value in determining the diagnosis of a case of tuberculous meningitis. The test depends on the oxidizing power of the permanganate, and is performed by titrating the spinal fluid

with a decinormal potassium permanganate solution. The spinal fluid in normal individuals or in those suffering from meningismus has little organic substance and the permanganate index is consequently low. In patients suffering from meningitis the organic substances are increased and the permanganate index is higher.

The author's case was that of a boy $7\frac{1}{2}$ years old. The history, clinical findings, and especially the course of the disease were suggestive of tuberculous meningitis, but all laboratory findings (with the exception of one doubtful Noguchi late in the disease) were negative, except the permanganate test, which showed an index of 3.4 at the first examination. This indicated a tuberculous meningitis and necropsy confirmed the diagnosis.

H. Sundt²⁶ quotes Calot to the effect that it would be better if physicians in charge of sanitariums for the tuberculous would think oftener of syphilis, and if syphilologists would think oftener of tuberculosis. Sundt is chief of the seashore sanitarium at Fredricksvern, and he says that in a comparatively large number of cases the patients sent to the hospital are not suffering from tuberculosis. In forty cases of hip joint disease admitted during the last three years, 27.5 per cent. proved to be nontuberculous, as also 20.7 per cent. of twenty-nine cases of diseases of the knee joint. In nearly all of the nontuberculous hip joint cases the trouble proved to be Perthers' juvenile osteochondritis deformans, and four out of the six of the knee joints affections were also syphilitic. Since the beginning of 1915, five of the twenty-two new admissions to the sanitarium responded positively to the Wassermann test. They had been sent in with the diagnosis of tuberculous disease of the hip joint, foot, knee or larynx.

The patients in the hospital were mostly children, and latent syphilis masqueraded as tuberculosis or "scrofula" in a surprising large number of cases, or accompanied cases of unmistakable tuberculosis. Sundt gives a description of several cases illustrating this point. One is as follows: A child, who had both knees affected after a trauma, had long been treated for tuberculosis and a destructive lesion in the palate had been treated for lupus. The tuberculin reaction was positive as was also the Wassermann reaction. Antisyphilitic treatment soon restored the child to health.

Other cases cited show that syphilis alone can induce the classical picture of "scrofula" in its typical form. All these patients presented merely the late manifestations of inherited syphilis. In none of them had it been recognized, but tedious treatment had been enforced for tuberculosis or lupus.

There are no absolutely reliable differentiating clinical signs; a primary localization of tuberculosis in the nasopharynx is of very rare

occurrence. The tuberculous lesions generally spread superficially, the syphilitic burrow deep. The tuberculin reaction is most instructive, when it induces a focal reaction, but this is rather an exceptional occurrence. When the findings are dubious, a course of antispecific treatment may decide the diagnosis, but it must be remembered that not everything which subsides under potassium iodid is syphilis. Moreover, the Wassermann reaction may be doubtful even with known syphilis.

E. H. Risley³⁷ has attempted by an analysis of a series of necropsy and clinical records to throw some additional light on the preoperative diagnosis of tuberculous mesenteric and retroperitoneal glands. The type of this disease which is secondary to general or intestinal tuberculosis is not considered, but only that type which has come to be recognized as a separate clinical entity.

Risley gives the following description of the disease, but his study did not enable him to add much to its preoperative diagnosis: The disease is extremely frequent in children, but by no means confined to this period, being nearly as common in young adults. As regards symptomatology, there may be no symptoms even in the presence of palpable glands. The condition may be discovered only at operation for some other condition, the glands being too small for palpation through the abdominal wall. Or there may be trivial symptoms, as fleeting but not severe right sided or general abdominal pain, with or without disturbance of digestion and bowel regulation. The general health is good or the patient is of the pale, "sickly" type. At times there is more or less constant, fairly well localized abdominal pain, with a soreness in the region of the cecum. Examination may or may not show the presence of resistance or an ill-defined mass. Or there may be sudden or gradual onset of, first, general, then localized abdominal pain, confined to the right lower quadrant. With the pain comes a rise of temperature, nausea, vomiting, constipation or diarrhea. Examination shows localized tenderness with spasm and resistance. The leukocyte count is between 12,000 and 15,000.

It is evident, then, that *tabes mesenterica*, like appendicitis, the lesion with which it is most often confused, gives a variety of symptoms and signs, none of them distinctive in themselves and from the analysis of which a preoperative diagnosis cannot be made.

SYMPTOMATOLOGY

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K. Fraser⁸⁸ has analyzed 296 cases of pulmonary tuberculosis among school children and makes important deductions from the results.

His statistics seemed to point to some relation between commencement of school life and the incidence of tuberculosis, and to the fact that school life has a prejudicial effect on children predisposed to tuberculosis. Children able to resist the attack so long as they are running about in the open air, break down when forced to spend a part of each day in stuffy overcrowded classrooms.

An inadequate increase rather than a failure to gain in weight is important. Closely associated with the question of weight is that of nutrition. The manifestations of impaired nutrition are many—pallor, anemia, weariness, loss of appetite. It is highly probable that defective nutrition is the first visible sign of tuberculous infection.

Night sweats in children may have no significance, and only, when they are described as cold and clammy, does the author attach any importance to them.

Cough as a diagnostic symptom is somewhat empirical, a persistent hard, dry cough is the type most to be suspected.

In regard to the localization of the lesion, one or both apices are usually involved. When only one apex is affected, it is more frequently the right, and, when both are affected, the right shows a more extensive lesion than the left.

Dulness is the most important physical sign. Inequality of breath sounds is an early indication of trouble, but the duration of this sign is short. Bronchial breathing is nearly always present and remains for an indefinite period. Friction and fine crepitant râles are the most significant accompaniments, and all accompaniments are suspicious, when persistent and localized.

Spontaneous improvement is more common in girls than in boys; from the sixth year the tendency to spontaneous improvement increases year by year. Children in rural districts show a very much greater tendency to spontaneous improvement than children in the cities.

J. P. Cullen³⁹ compares pulmonary tuberculosis in childhood with phthisis of adult life and finds the path of infection is identical. In both, the terminal bronchioles are the portal of entry. In the adult, possibly because of a blocking up of the lymph paths by a previous tuberculosis or mechanical irritation, the bacilli remain localized and produce a bronchiolitis or bronchopneumonia, which undergoes the usual changes of caseation, fibrosis, calcification, or softening. In childhood the infection does not remain localized; the lymphatics are involved, and a definite infection occurs along their entire course.

Signs and symptoms depend on the point of arrest of the bacilli. In the adult type this is at the beginning of the journey and local symptoms, like cough, expectoration, hemoptysis, are those for which the patient usually seeks advice. Physical signs, due to the situation of the lesion, are sufficiently well marked to facilitate an early diagnosis by the usual methods.

In childhood local symptoms are indefinite. There may be reflex cough and vomiting. General symptoms are more marked. The patient is languid and anemic and may suffer from night sweats or slight evening pyrexia. Growth and nutrition are interfered with. Physical signs, because of the depth of the lesion, are by no means obvious.

Enlargement of the normal interspinous, dulness with prominent venules over the region from the first to the fifth dorsal spines, crepitations in the nipple region, and harsh cogwheel sounds at the apices are the sounds which suggest further examination—as by means of the Roentgen-ray.

Adult and infantile phthisis are therefore one and the same disease. The difference in their symptoms and signs are explicable on anatomic peculiarities. The affection in childhood may remain limited to the lymphatics and then the prognosis is good, provided the disease is recognized early and treated properly. Diagnosed wrongly or too late, the parenchyma of the lungs becomes involved and the case passes on to the adult variety with slight chance of recovery.

According to O. W. McMichael,⁴⁰ our knowledge of early manifestations of tuberculosis in childhood must come from the formation in our minds of a composite picture, resulting from systematic study of large numbers of children who have been in contact with open cases of tuberculosis. This opportunity is offered in our Municipal Tuberculosis Dispensaries, where it is the custom to examine systematically all members of the family where one member is found to be tuberculous.

Inasmuch as the first resting place of the tubercle bacillus is always in lymphoid tissue, it is to the glands that we must give our first attention in the examination of children for tuberculosis. Glandular enlargement is found in nearly all children who are in contact with open cases of tuberculosis, while this is universally true of children so exposed, it is also true that these glands are enlarged in nearly all children. The presence of enlarged glands by no means prove tuberculosis. Hypertrophy of glands is evidence of combat against infection, and, if there is any distinction between the glands of tuberculous children and the enlargement of glands due to other infections, it is that in tuberculosis the palpable glands are smaller and firmer than those of nontuberculous children, and may be traced along the course of lymphatics as small, firm beads. These glands tend to disappear as the evidence of pulmonary involvement increases, so that, in children with extensive pulmonary involvement, the glandular enlargement may be very slight and distinctly less than the enlargement in the average normal child. The author has come to regard the disappearance of glandular enlargement without the development of pulmonary signs as evidence that the condition was nontuberculous, and, in tuberculous children, the shrinking of the glands with an increase in their density as evidence of favorable progress toward control of the disease.

The tendency to regard anemia and malnutrition as evidence of tuberculosis is very likely to lead to error, for, in family groups of children known to be exposed to open cases of tuberculosis, it is exceedingly common to find that the best nourished and least anemic

looking children are the ones who present the most signs of tuberculous disease.

One of the first things noticed by the parents is that the child stops growing. The tuberculous child is usually undersized and underweight. The posture in standing is relaxed and the alae scapulae are prominent in nearly every instance. The hair and skin are dry in children who show pronounced signs of the disease. No matter how well nourished, the tuberculous child has a weary expression about the eyes, the lower lid may droop sufficiently to show a line of sclera below the cornea, and McMichael has long noted a bluish-pink triangle with the lower lid as its base, which he regards as a distinct sign of tuberculosis in children.

The pupils of the tuberculous child are usually dilated. If the pupils are unequal one may suspect pulmonary activity on the side on which the dilation is more marked.

In examination of the chest, attention is first drawn to dilation of the superficial veins, usually denoting marked enlargement of the mediastinal glands. A further evidence of this enlargement is Smith's sign, which consists of a systolic murmur heard at the right border of the manubrium when the head is thrown back. The chest examination differs little from that of the adult, with the exception that it reveals the greater frequency of tuberculous deposits in the bases of the lungs in children than in adults. The more general the bronchitis, the less likely is this an evidence of tuberculous disease, while fine moist râles confined to a small area in the lung may be regarded with grave suspicion.

McMichael thinks that no matter how expert one may be in the interpretation of physical signs, more direct evidence of tuberculous disease can be obtained by the use of tuberculin than by any other means. The v. Pirquet skin reaction has the same significance in adults as it has in children. The mere statement that a v. Pirquet reaction is positive or negative gives little information, but the character of the reaction gives valuable information regarding defensive processes going on in the blood of the patient. A poorly nourished child under 1 year of age in the arms of a tuberculous mother will usually give a negative v. Pirquet reaction. A tuberculous patient who gives a slight reaction will, after the continued administration of some preparation derived from the tubercle bacillus, give reactions of increasing intensity which coincide with other physical signs of improvement, and, on the other hand, the tuberculous patient who is losing ground will show reactions of decreasing intensity and will finally fail to react at all. A negative reaction in a child is not conclusive evidence that the child is nontuberculous any more than a positive reaction is evidence that the child is the victim of tuberculous disease. The value of the reaction is dependent on the skill of the observer.

The use of tuberculin in the treatment of children promises more than does any other remedial measure. Children bear large doses of tubercle protein better than adults, and, to stimulate the production of immunity, appreciable doses must be given. This is especially true where operative procedures are contemplated and where the blood of the child must be capable of taking care of any tubercle bacilli that may be squeezed out into the circulation by the manipulation incident to the operation. It is unwise to undertake any surgical procedure until a child can endure a dose of 0.4 or 0.5 milligram of tubercle protein without severe reaction.

While working at the Woolwich Tuberculosis Dispensary, J. M. Campbell⁴⁸ placed tuberculous children in four groups. In the first, or suspect group, were all who, on repeated examination, showed physical signs in the chest, such as poor expansion at one or the other apex or of one lung generally, with impaired resonance over the same area, and weakened air entry. In this group were also placed children who showed the stigmata of tuberculosis and who were living in homes where there was an adult with open tuberculosis.

In the second group were placed those in the incipient stage, the most difficult to diagnose. In many instances there were no more physical signs than in the cases of the first group, but there was evidence of toxemia. The child was pale and had lost weight; there was sometimes a short cough and sweating at night. The temperature curve varied more than normal. Among the physical signs on which the author laid stress were granular or "sticky" inspirations, the presence over the suspected area of fine râles, which did not disappear on coughing, and a positive v. Pirquet test.

The third group includes cases of caseous and fibrocaseous tuberculosis. The signs and symptoms in these were very similar to those found in adults—but the lesions were less often apical and frequently more extensive at the root of the lung or at the base. The toxemia in this form was less marked in children than in adults and in the fibrocaseous form contraction of the lung caused little inconvenience to the child.

In the fourth group were placed cases of tuberculosis of the bronchial glands and of hilus tuberculosis. These formed a fairly large group and gave definite signs and symptoms. There was usually an indefinite and progressive condition of ill health in a child who had been healthy. There was anemia and lassitude; the muscles were flabby, and the child suffered from a troublesome paroxysmal cough. Physical signs were found only when there was pressure on a bronchus which prevented inflation of the lung.

The writer decries the tendency definitely to label too many children tuberculous. She thinks it necessary to revise and standardize

the nomenclature of tuberculosis, and that until this is done there will be much indiscriminate notification of cases to the detriment of the child.

B. S. Pollak⁴⁴ calls attention again to the similarity of tuberculosis and syphilis. He says that in tuberculosis as well as in syphilis there is a primary stage with primary symptoms and regional lymphatic gland involvement, a secondary stage which runs through a course of years with tendency to relapses, and a tertiary or late stage which is known as phthisis pulmonalis. Also, tuberculosis, like syphilis, causes immunity against reinfection.

H. Koch⁴⁵ defines the early stage of infection with tuberculosis as the period between the day of infection and the time when the v. Pirquet reaction becomes positive. By a systematic application of the v. Pirquet test Koch was able to determine this early stage in three patients, and by careful study of their symptoms he attempted to find clinical signs which would offer a possibility of diagnosis of this stage.

His three cases were as follows: *Case 1.*—An infant was admitted to the hospital three hours after birth. The mother had advanced tuberculosis. In the eighth week at the hospital the child developed a temperature and in the ninth the cutaneous test became positive. *Case 2.*—An infant three weeks old was admitted to the hospital. The v. Pirquet test was negative. In the seventh week there was a rise in temperature and the v. Pirquet test became positive. *Case 3.*—A four and a half year old boy was brought to the hospital because of a non-tuberculous inflammation of the hip joint. He ran a temperature for two weeks. The v. Pirquet test was negative when the boy was admitted, was repeated systematically, and became positive after three months.

The three patients had only one symptom in common—a rise in temperature at the time the v. Pirquet test became positive. The type of temperature corresponded to that found in the last stages of the disease, namely, an evening rise with a morning remission. The author calls this febrile reaction the initial fever of tuberculosis. In spite of careful observation, no other symptoms were found, and there were no local signs, due to the pulmonary lesion or involvement of the regional bronchial lymphatic glands. But in Case 3 the Roentgen-ray pictures taken after the infection, showed a more marked and widespread shadow at the left hilus than the first one taken before the infection.

It is evident that systematic tuberculin tests and measurement of temperature can not be made on healthy children, but to make them on children who remain a long time in hospitals and are exposed to tuberculous infection would be of theoretical interest and of value. These children should be watched for the onset of the infection and for

clinical symptoms during its early stages. In the writer's cases the initial fever and the positive v. Pirquet test occurred in the seventh week after the infection.

H. Bergmann⁴⁹ reports a case of advanced pulmonary tuberculosis with cavity formation in a 2-months-old child whose mother had died of tuberculosis shortly after his birth. The child was brought to the hospital March 2, 1914, with a history of having coughed since birth. He had never been nursed. Examination showed a poorly nourished baby, with a temperature running between 36.6 and 39.2 C. Over the left lower lobe posteriorly were large moist râles. The v. Pirquet test was positive. The child died March 22, 1914. Necropsy showed the following: Both lungs were adherent to the thorax at the apices; over the visceral pleura were many miliary tubercles. In the upper part of the right lung was a large walnut-sized cavity with pus-like contents, besides many small pea-sized cavities. Throughout the entire lung were small and large partly caseated tubercles. In the lower part of the upper lobe of the left lung were two cavities, and scattered throughout this lung also were many caseated tubercles. The bronchial glands were enlarged and caseated. One kidney and also the cecum contained many miliary tubercles.

In discussing the case, Bergmann first considers the positive tuberculin test in so young an infant. He quotes Friedberger and Simmel, who found in newly born sensitized guinea-pigs a pronounced hyp sensitiveness to a reinjection, and Rietschel, who thinks that antibodies can be carried from the mother to the fetus, but exist only a short time, and Schanz, who also has shown that antibodies can be carried from the mother to the offspring in guinea-pigs, but are soon lost. Bergmann, then, believes that the child of a mother who gives a positive tuberculine test, will also give a positive reaction soon after birth, but for a few days only. If the child is tuberculous, the positive reaction will reappear.

Of the pathologic findings, Bergmann notes especially that the lungs were widely diseased and the other organs hardly affected at all. He thinks the case one of congenital tuberculosis hematogenous in origin, and explains the extraordinarily severe manifestations by the active functioning of the lungs at birth.

F. Hall⁵⁰ reports a case of rapidly advancing pulmonary tuberculosis in a 2-year-old child, whose mother was known to have the disease since its birth. The child had been breast fed by the mother for thirteen months. When 6 months old she contracted pneumonia, complicated by otitis media, but apparently she made a complete recovery and remained well until two weeks before entrance to the hospital, during which time she had been quite ill. There had been a discharge from the eyes,

nose and ears; she had had elevated temperature, had coughed considerably and had lost weight.

The diagnosis on entrance as far as the lesion in the lungs was concerned, was a diffuse bronchitis, but the Roentgen ray made evident the presence of a tuberculosis, and as the disease progressed, showed its extension from the hilus into the lobes. This was more marked in the right lower lobe. The Roentgen-ray picture showed also the presence of a cavity at the left hilus before it was evidenced by physical signs. The cavity formation was confirmed at necropsy.

The v. Pirquet test had given a marked reaction early in the disease. It became faint as the child became weaker, and absent a few days before death. Tubercle bacilli were not found until late in the disease, when the diagnosis was well established. They were found first in the stools, then in the sputum.

H. Barbier⁵¹ reports a case of acute tuberculous alveolitis in a 3-months-old infant, who was moribund when brought to the hospital. At necropsy the lungs were congested and had the appearance of being filled with miliary tubercles. There was also a caseous bronchial adenopathy.

Histologic examination showed an intense alveolitis, intra-alveolar exudation and infiltration of the thickened alveolar walls. The exudate was composed of amorphous material resulting from necrosis of the alveolar epithelial cells. In some places there was complete destruction of the alveolar walls. Sections stained by the Ziehl method showed an enormous number of tubercle bacilli within the alveolae, and in the necrotic tissue of alveolae. Barbier believes that in this case the infection took place by inhalation.

F. Weihe⁵² has made an interesting clinical and roentgenologic study of interlobular pleuritic exudates in children. He does not agree with Eisler, who attributes these exudates always to a tuberculosis, but believes they are often metapneumonic in origin. Of a series of eight cases, observed within two years, there was only one which he regarded as tuberculous. This patient was a 3-year-old, emaciated boy who had a tuberculous involvement of the larynx as well as marked signs in the lungs. The Roentgen-ray picture showed a widening of median shadow and irregular shadows scattered through the right pulmonary field. On the right side, running from the right rib upward to the fifth, was also a sharply defined linear shadow, which evidently represented an old interlobular exudate.

In all the other instances the children were acutely ill. There was a high evening temperature, with a morning remission. This febrile period lasted from eight days to three weeks and usually ended abruptly. The few pulmonary findings contrasted sharply with the

severe general condition. Sometimes a band of dulness was found on percussion in the axillary region. In the author's cases the exudate was usually on the right side and the Roentgen-ray picture showed a horizontal shadow, the thickness of a lead pencil, beginning at the lower border of the fifth rib in front and ending at the lower border of the fourth rib laterally. In some instances after the shadow had run about one-third of its course, it spread out fan-like and formed a triangular shadow on the chest wall. Repeated pictures showed that these shadows absorbed rapidly.

Whenever the exudate could be outlined by percussion or by the Roentgen ray, an attempt at puncture was made. In four cases this was successful and small amounts of cloudy pus were obtained.

Weihe then divides interlobular exudates into two groups, the metapneumonic and the tuberculous, and he is not sure that it is always possible to differentiate between the two. He thinks, however, one point in differentiation is that tuberculous exudates absorb with difficulty, while metapneumonic exudates absorb quickly and their shadows are seen to disappear in a series of Roentgen-ray plates.

E. Germonig⁵³ reports a case of tuberculous pharyngitis in a 22-months-old infant. There was no case of tuberculosis in the child's direct family, but one sister of the mother had died of the disease. Examination showed a fairly well developed infant. The muscles were flabby and there were enlarged glands on both sides of the neck. The lungs were resonant throughout and the breath sounds were sharp and rough, especially over the lower lobes posteriorly. The Roentgen-ray picture showed a dark area at the hilus of the right lung, which evidently corresponded to a group of bronchial glands. In the throat there was ulceration of the uvula, hard palate, and palatoglossal arches. The epiglottis was much thickened. Examination of the larynx was impossible, but from the clear cry of the child, it was evident the vocal cords were intact. The v. Priquet test was positive. Microscopic examination of a small piece of tissue excised from the uvula gave a picture typical of tuberculosis. No tubercle bacilli were found.

D. S. Wilson⁵⁴ reports the case of laryngopharyngeal stenosis, complicating pulmonary tuberculosis in a 16-year-old boy. The unusual feature of the disease was that the base of the tongue, the epiglottis, the pharynx, and the larynx were incorporated in a mass of adhesions. The aperture through the pharynx to the esophagus was reduced to about the size of an ordinary lead pencil. It had become impossible for the boy to swallow, and liquids, instead of reaching the esophagus, regurgitated through the mouth and nose. Respiration was seriously impaired by the stenosis and the whistling sound produced by the boy's breathing could be heard for a considerable distance.

A. E. Meyers⁵⁵ analyzed 105 cases of tuberculous meningitis, because from textbook descriptions it is difficult to estimate the frequency of the various signs and symptoms.

Of the 105 patients, fifty-three were females, fifty-two males. Over 30 per cent. were between 2 and 3 years of age, and over 80 per cent. between 18 months and 5 years. Most of the cases occurred in June, July and January. Measles was mentioned in the past history of twenty-seven patients or 26 per cent.; whooping cough in 22 per cent. Thirty-eight per cent. had had no previous infectious disease.

The average duration of the disease was seventeen days. The average period in the hospital five and eight-tenths days. This varied directly with the number of lumbar punctures. Tubercle bacilli were found in the spinal fluid in 21.5 per cent. of the cases. The fluid was under pressure in 80 per cent. The average cell count was 198 cells to the cubic millimeter. The prevailing type of cell was the small mononuclear ranging from 90 to 100 per cent. in 67 per cent. of the cases. In three cases the polymorphonuclear leukocyte was the prevailing type of cell. A fibrin clot was present in 70 per cent. of the cases. A positive globulin test was obtained in 50 per cent. of the cases; in 7 per cent. it was negative; and the test was not mentioned in 43 per cent.

The lowest white blood cell count was 8,500, the highest 48,000. The largest percentage of cases showed a count between 10,000 and 15,000.

Of the cases in which a v. Pirquet test was performed 63 per cent. gave a positive reaction, 25 per cent. a negative and 2 per cent. a suggestive reaction.

There was a definite history of direct exposure to tuberculosis in 25 per cent.; no known exposure in 73 per cent. and no record of exposure in 2 per cent.

In 30 per cent. of the cases there were sufficient signs in the lungs to show they were involved in the tuberculous process. In two cases d'Espine's sign was noted.

In 71 per cent. of the cases the eye reflexes were abnormal. In over 30 per cent. the patella reflexes were equal and active; in 21 per cent. they were absent; in 5 per cent. they were equal and sluggish; in 6 per cent. they were irregular; in 6 per cent. they were not mentioned; in 32 per cent. they were equal and normal. There was a positive Babinski sign in 21 per cent.; a negative in 55 per cent. The condition was not mentioned in 24 per cent. Abdominal and epigastric reflexes were positive in 14 per cent., negative in 17 per cent. and not mentioned in 69 per cent. Brudzinski's sign was positive in 40 per cent. Kernig's sign was present in 27 per cent. Forty-three per cent.

of all cases showed some kind of paralysis. Rigidity of the neck was present in 70 per cent. of the cases.

Thirty-nine of the patients had convulsions before entrance; forty-five were unconscious on entrance. In practically every history drowsiness, apathy, mental dulness, languor, irritability and sleepiness were mentioned. In over 85 per cent. vomiting was recorded as an initial symptom. Pain was a comparatively frequent symptom. Headache was present in 17 per cent. In 50 per cent. there was a history of constipation. Grinding the teeth, restless sleep, delirium, loss of sphincter control, crying, capricious appetite and inability to swallow were symptoms frequently mentioned.

In 41 per cent. of the cases there was a final rise in pulse, temperature and respiration curves. A definite remission of symptoms with a corresponding drop in pulse and temperature occurred in 64 per cent. There were no recoveries.

C. O. Hawthorne⁵⁷ discusses localizing brain symptoms in tuberculous meningitis and reports two cases. He says that occasionally tuberculous meningitis has an abrupt onset, and that this may take the form either of localized palsies or localized convulsions. His first case was that of a boy 10 years old who had at one time had some enlarged glands, but otherwise a negative history. On September 18 the child was said to have been sick while at school, but on the two following days was as active as usual. During the night of the twentieth he again vomited and in the morning examination showed a paralysis of the left face and left upper limb, which disappeared within the course of forty-eight hours. On the following day there were repeated convulsive seizures, limited to the left limbs, and inability to speak. On the cessation of the convulsions, left hemiplegia was again observed. Later the paralysis entirely disappeared, but headache, persistent vomiting and temperature remained and these with the finding of abundant cellular elements in the cerebrospinal fluid left no room for uncertainty in the diagnosis of tuberculous meningitis.

The second patient was a boy 1 year and 7 months old. He was suddenly seized with convulsions, which were strictly limited to the right side. These ceased in an hour or so. There was no paralysis or evidence of organic disease and the cerebrospinal fluid was free from excess of cells and micro-organisms. Two days later the convulsions recurred and the child gradually developed characteristic signs of tuberculous meningitis. The diagnosis was confirmed by necropsy.

Hawthorne offers as an explanation of the unusual onset in these cases that from some primary source as the mediastinal glands, an embolus or multiple emboli reached the brain through the blood stream. It is not difficult to see how this sudden blow might be followed by a local recovery of nerve function, with consequent disappearance of the

convulsions and paralysis. The subsequent appearance of the signs of a generalized meningitis must be explained by a tendency of the specific irritant to produce a gradually extending infection.

H. Brockmann⁵⁸ reports two cases of pseudomeningitis in tuberculous children, offering great difficulty of diagnosis. The first was that of a 2-year-old boy, with a family history of tuberculosis. The child had always been well until three months before his admission to the clinic, Feb. 28, 1914. For the previous week, he had been restless, slept badly, cried a great deal and had frequently put his hand to his head.

Examination showed a relatively well nourished child. Scattered over the body were many small papular tuberculids. There was an infiltration of the left apex with weakened respiration and moist râles. The v. Pirquet test was at first doubtful, later weakly positive. There were also symptoms which pointed to involvement of the central nervous system. Marked hyperesthesia, sensitiveness to light, tense and bulging fontanel, right convergent strabismus, obliteration of right nasolabial fold, pronounced rigidity of the neck, paresis of right upper and lower extremities, hypertonia in all, especially in both right extremities, patellar reflex increased on the left side, diminished on the right, patella clonus increased on both sides.

Lumbar puncture March 2, gave a slightly cloudy fluid, under pressure, albumin content six lines, according to the Niszl method. In the sediment were many lymphocytes but no tubercle bacilli could be demonstrated. On the basis of these clinical findings and of the characteristics of the spinal fluid, the writer made a diagnosis of tuberculous meningitis and at the same time suspected the existence of a tubercle, localized in the left hemisphere, and explaining the right sided hemiplegia which had existed three months.

The child's condition remained stationary for months. For several weeks 50 c.c. of fluid were withdrawn every second day, always showing the same inflammatory changes. Twice it was injected into guinea-pigs, but the animals lived. This unusual course caused the writer to abandon the diagnosis of tuberculous meningitis and make one of solitary tubercle situated in the left ventricle, which, by inflammatory irritation caused a rich secretion of lymphocytes and albumin. The child died September 21, and necropsy confirmed the diagnosis. In the neighborhood of the left cerebral ganglion was a conglomerate tubercle pointing toward the enlarged cerebral ventricle. There was also a marked internal hydrocephalous and a fresh crop of miliary tubercles on the meninges, but no evidence of a healed meningitis.

The second patient was a 9-weeks-old child, also with a family history of tuberculosis, admitted to the clinic Oct. 23, 1914. The baby was well nourished; scattered over the body were many small papular

tuberculids. The upper and middle lobes of the right lung showed well marked infiltration. The v. Pirquet reaction was positive. The fontanel was tense and there was pronounced hypertonia of the lower extremities, with increased patella reflexes. Lumbar puncture yielded a clear fluid under high pressure, but with a normal albumin content and no increase in lymphocytes. No tubercle bacilli were found and animal experiments were negative. Necropsy showed wide-spread tuberculous changes in the lungs and caseation of the bronchial and mesenteric glands. The brain and inner membranes were normal; the dura showed patches of pachymeningitis.

Both these cases gave a clinical picture of tuberculous meningitis. In the first it was produced by a giant tubercle in the neighborhood of the cerebral ventricle, which had given rise to localized inflammation of the ventricular wall. In the second it was caused by a meningismus, due to the tuberculotoxic products.

The author urges that caution be exercised in making a diagnosis and giving the prognosis in conditions which simulate tuberculous meningitis, for complete cures can be effected in such as he cites.

E. B. Friedenwald and W. Greenfeld⁵⁹ report an unusual case of tuberculoma of the brain in a 7-year-old colored boy. The child was first seen in June, 1912, when he had had a convulsion. Other convulsions, epileptiform in character, always beginning with spasm of the right arm and leg, followed at irregular intervals. During the summer the convulsions became more and more frequent, the child's appetite failed, and he lost weight rapidly. Toward the end of autumn the convulsions became very violent. On Jan. 11, 1913, after a violent convulsion, the patient became acutely ill, the temperature rose, the respirations became rapid. Patches of crepitation were found over the whole right lung. On the twenty-first the abdomen became rigid and contained fluid. The child died Jan. 24, 1913.

Necropsy showed caseous pneumonia of the right lung, fibroid apex of left lung, tuberculous peritonitis, and tuberculous bronchial glands, and small tuberculous foci in the liver. The most interesting changes were in the brain, in both hemispheres of which a number of dense, whitish, grayish masses were embedded. The left cerebral hemisphere contained a number of conglomerate foci forming a large mass, situated in the ascending parietal and superior marginal and superior parietal convolutions. The right cerebral hemisphere contained four masses, one in the upper part of the mid frontal convolution, one in the lower part of the external surface of the occipital lobe, the third in the parieto-occipital sulcus, and the fourth, extending across the limiting sulcus, involved the upper part of the insula, the claustrum and external capsule. Histologically the masses showed the ordinary changes produced in tuberculosis, but most unusual were the masses of tubercle

bacilli found in the vessel walls and in the caliber of the vessels of the brain and bronchial lymph glands. (The authors could discover in the literature no other instance of tubercle bacilli found in the blood vessels.)

The original focus the authors think was the fibroid apex of the left lung or the tuberculous bronchial lymph glands, from which the infection was carried to the brain. The twitching of the right arm and leg was explained by the tumor in the left ascending parietal convolution.

L. Guthrie⁶⁰ reports a case of tuberculoma of the pons varolii in a 3½-year-old boy. The child was admitted to the hospital Feb. 2, 1915, a year after an attack of pneumonia. He was gradually losing weight, his cheeks were frequently flushed, and a cough, which had been present on and off since birth, had become worse. Strabismus had developed in the left eye ten days before admission.

Examination on admission showed a thin, feeble child with a dusky flush on his cheeks. He was dull and apathetic but intelligent. The chin constantly deviated toward the left side and the head toward the right shoulder. The optic disks and fundi were normal, but the left eye was strongly turned inward. No outward movement beyond the median line was possible. Power of inward movement of the right eye was also lessened. There was complete paralysis of the left side of the face. Apparently only the left sixth and seventh cranial nerves were paralyzed. There was no spasticity of the lower extremities, but the knee jerks were rather more active on the right than on the left side. The left apex was dull on percussion, the breath sound over this area was almost amphoric in character and accompanied by loud, coarse râles. Many râles were heard over both bases. The v. Pirquet test was markedly positive.

The child lived six weeks after admission and showed slight change of condition. At necropsy the pons was found to be occupied in its center by a tuberculous mass about 1 inch in diameter. As the brain was removed from the base of the skull, a small, soft, caseating tumor about the size of a cherry was left attached to the cribriform plate of the ethmoid. Two or three similar masses were found just beneath the cortex of the frontal lobes. Throughout the lungs were many miliary tubercles. The bronchial glands were distinctly tuberculous.

De Stefano⁶¹ reports a case of tuberculous cardiocirrhosis in a child of 10 years. For two years she had had febrile symptoms and headache, followed by abdominal swelling. For one year she had had strabismus and convulsive attacks repeated at long intervals. On admission to the hospital examination showed cyanosis, an enlarged and hard abdomen with a palpable spleen. The precordial region was prominent and increased in size. The bases of both lungs were dull, with weak

vesicular murmur and absence of vocal fremitus. There was also dulness in the right supraspinous fossa with weak inspiration. There were drowsiness, increased patella reflexes, and a positive cutaneous reaction. The Wassermann reaction was negative. At necropsy there was found a polyserositis, universal pericardial adhesions, nutmeg liver and tuberculous masses in the brain. The case may be considered one of polyserositis, causing pericardial adhesions and nutmeg liver.

H. Barbier⁶² describes a form of tuberculosis of the liver in children suffering from hereditary tuberculosis, analogous to hereditary syphilis of the liver. The liver in these cases shows extra- and intralobular perivascular sclerotic changes accompanied by fatty degeneration of the liver cells. The chief characteristic, however, is the hypoplasia. In some cases the degree of hypoplasia of the liver corresponds to the degree of atrophy in the child; in others it exceeds it. In almost every case miliary tubercles or confluent tuberculous nodules are found associated with the above changes.

Barbier reports a case of this form of hepatic tuberculosis. The patient was a 3½-months-old infant whose father had tuberculosis. The child had seemed well for a month and a half, when it had ceased to gain in weight. For two months before entering the hospital he had suffered from cough, vomiting and fever. He was in the hospital ten weeks and during that time there was a diffuse bronchitis, anorexia, and emaciation. At necropsy there was found a caseous bronchopneumonia and a generalized miliary tuberculosis. But what was most striking was the aspect of the liver. It was small (165 gm.), yellow and literally riddled with tubercles, the size of millet seeds. Microscopically there were many caseated tubercles and a number of the hepatic lobules were completely caseated. There was a diffuse hepatitis with cellular necrosis, but the liver cells did not show fatty degeneration. Very remarkable was the great number of tubercle bacilli in the center of the nodules.

E. Feer⁶³ has studied the small papular tuberculid which occurs in children and he is surprised at its frequency. The eruption consists of slightly raised papules, usually 1 or 2, rarely 3 or 4 millimeters in diameter, which do not itch. In the center of the papule is a brown scale or depression. The waxy glistening character of the wall around the central scale or depression is quite characteristic and is noted especially by reflected light or when the skin is put on a stretch. Suppuration of the center of the papule makes a differential diagnosis from acne difficult. The lesion may last weeks and then disappear completely, or leave a flat scar.

Papular tuberculids are usually few in number and occur on the thigh, in the groin, in the gluteal region, and on the extensor side of

the arm. They are found more often in younger than in older children—and more frequently in infants. They are the result of embolism, either of tubercle bacilli or of toxic products. In one instance Feer found tubercle bacilli in histologic sections and produced typical tuberculids by inoculation of the material into guinea-pigs.

The finding of papular tuberculids usually signifies that an active tuberculosis is present.

TUBERCULOSIS OF THE TRACHEOBRONCHIAL GLANDS

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E. Rist⁶⁴ asks: 1. What trace is found in the adult of glandular tuberculosis of childhood? 2. How account for the difference between the lesions of the bronchial glands of the child and those of the adult?

He says that the relation between the pulmonary and glandular lesion in the child and adult are reversed. In the adult, extensive ulcerative tuberculosis of the lungs is generally found postmortem, coincident with bronchial glands of normal size, and vice versa in the child. Instead of being fixed to the surrounding tissues by strong fibro-adhesive bands, the glands are easily enucleated, and, what is more important, they are rarely affected by caseous degeneration as are those of the child. Moreover, most of the glands in the adult contain small hyalin masses often anthracotic and partly calcified. Rist thinks it is incorrect to assume that these glands have become sclerotic and are unable to react to any infection, for they do react to any disease except tuberculosis. Nor does he think that caseation of the bronchial glands is a specific characteristic of tuberculosis of the bronchial glands of childhood, but of a primary tuberculous infection. If pulmonary tuberculosis in the adult is not accompanied by caseation of the corresponding glands, it is because the pulmonary

tuberculosis in the adult is a reinfection. Caseation is not specific of tuberculosis of childhood, but of primary tuberculous infection.

W. W. Howell⁶⁸ has attempted to ascertain the frequency of chronic inflammation of the bronchial glands in infancy and childhood, also the reliability of signs of enlarged glands, and their possible pathology. With these objects in mind he examined for enlarged bronchial glands all the children who came under his care during one year. There were over 300 babies under 2 years admitted to the Infants' Hospital, 500 schoolchildren between 6 and 13 years, and patients in private practice.

The means used to determine the enlarged glands was auscultation, i. e., the determination of D'Espine's sign, and percussion. The Roentgen rays were used to confirm the physical findings.

From his examination Howell accepted as a positive D'Espine a change in character of whispered voice sounds (in older children) or of the expirium during crying spells (in infants) at or below the third dorsal vertebra. He found percussion of the glands difficult, but dulness in the second interspace to the right of the sternum and dulness to the right of the vertebral column at the level of the spine of the scapula was definite and significant and agreed pretty well with the intensity of D'Espine's sign. The roentgenograms of patients with positive physical findings always showed shadows.

The author says there is a general belief that chronic bronchial adenitis means tuberculosis, and, while this may be true in infancy, this study has led him to believe it otherwise in older children. He thinks that in older children, if the enlargement of the glands is accompanied by anemia and malnutrition, the underlying condition is probably tuberculosis, but, as he frequently found enlarged bronchial glands in well nourished children with carious teeth, enlarged tonsils and adenoids and a chain of palpable crevical glands, he thinks these conditions are factors in the production of the enlarged bronchial glands.

T. Frazier⁶⁹ reviews the main diagnostic points on which the recognition of tuberculous bronchial glands depends. He thinks the history and symptoms are as important as the physical signs, if not more so. The history of exposure to infection or of an attack of measles, whooping cough, or influenza, with the nature of convalescence, is to be considered.

In the beginning of the disease the symptoms may be very indefinite. Loss in weight, or a stationary weight, is the most significant constitutional symptom. Pallor of the face and mucous membranes may appear so gradually that it is not noted until it has existed some time. There is a loss in strength and the child shows evidence of malnutrition and becomes languid and fretful. A cough is usually present, although there is no particular type of cough characteristic of tuber-

culous bronchial glands. In younger children it may be spasmodic, resembling whooping cough; in older children it is likely to be dry and unproductive.

The significance of enlarged cervical glands is not so great as it was once thought to be. Lymphoid activity is great during childhood and palpable lymph glands are the rule.

The v. Pirquet skin reaction has a decided value, especially in younger children.

The examination of the chest in children is often unsatisfactory and a diagnosis of tuberculous bronchial glands is arrived at with great difficulty. In the early stages there may be no physical signs, although the disease is active. In older children there may often be seen, when a deep breath is taken, the so-called hilus dimple, a depression anteriorly in the inner part of the upper two interspaces. The most constant sign on percussion is a slight dulness in the interscapular region. D'Espine's sign is of no importance unless it is heard below the level of the first or second dorsal spine in a child of 8, or below the third or fourth in a child of 12. Fine râles about the nipple are found in a number of instances.

Although none of the physical signs are absolute in their significance, the presence of dilated veins, interscapular dulness, whispered pectoriloquy beyond the normal limits gives the suspicion of tuberculous bronchial glands. The suspicion is strengthened if the child exhibits any or all of the symptoms mentioned.

E. Rach⁶⁷ adds another contribution to those he has already written on the diagnosis of tuberculous bronchial glands in children.

Rach agrees with other writers that in children, the glands in the right tracheobronchial space are the ones most frequently affected in this condition. Since his last report he has seen a great number of Roentgen-ray pictures of tuberculosis of these glands and has been able to verify the pictures anatomically. These pictures exhibit a uniformity worthy of note. The shadows representing the enlarged glands runs parallel with that of the trachea, and, above and below, joins the median shadow. The shadow is usually date or club shaped.

However, Rach does not believe that a diagnosis based only on radiologic findings is satisfactory, and he discusses a group of symptoms, due to pressure of the glands on neighboring structures, which, when taken with the Roentgen-ray pictures, is very significant.

This group of symptoms has frequently been described in the literature. Rach quotes Barthez and Rilliet, who mention rough paroxysmal cough, asthmatic attacks, hoarseness, without laryngeal involvement, from pressure on the nerves; intermittent cyanosis and edema of the face from pressure on the superior vena cava; and expiratory stridor from pressure on the trachea and bronchi.

The expiratory stridor seems to be one of the most important symptoms. It has been described by Schick as follows: It is heard during the entire expirium, more easily when the child is at rest. The expirium is lengthened and dyspneic—the inspirium barely audible. After a while the expiratory difficulty causes an emphysema of the lungs. On necropsy Schick found that the stridor was caused by compression of a principal bronchus by cheesy, enlarged lymph glands. Its expiratory character is due to the fact that during inspiration the bronchial tubes dilate and allow the air to enter, while during expiration the bronchial tubes collapse and increase, by the pressure of the enlarged glands, the obstruction already present. The reason for the occurrence of the expiratory stridor in young children only is that, after the first year, the bronchial tubes lose their elasticity and do not dilate and collapse so readily.

Rach, after the study of forty-one cases of enlarged bronchial glands, draws the following conclusions: Enlargement of the right tracheobronchial glands gives, in Roentgen-ray plates, a date- or club-shaped shadow, which bends outward from the median shadow and runs parallel with the trachea. In consequence of their topologic relations, these glands can cause distinct clinical symptoms by compression of the neighboring structures. In infants, compression of the right principal bronchus causes a crowing expiratory stridor, in older children a pertussis-like cough. These symptoms in conjunction with a positive cutaneous reaction and the characteristic radiologic findings, are sufficient to make a diagnosis of tuberculous bronchial glands.

H. F. Stoll⁶⁸ has made a study of D'Espine's sign of enlarged bronchial glands. In 1907 D'Espine drew attention to a sign that he had observed for many years and considered diagnostic of enlargement of the bronchial glands. He stated that in young children the whispered voice normally ceases at the level of the seventh cervical spine posteriorly. When, however, there is enlargement of the lymph nodes and the patient whispers "thirty-three," bronchophony is heard over the upper thoracic spine as well.

Stoll has had a limited opportunity to compare this sign with the postmortem findings. In a few patients not presenting any increased whisper sounds no enlargement of the bronchial glands was found. Four patients exhibited a marked D'Espine and all had large bronchial glands.

One case was of especial interest. The patient was a 10-year-old child sent to the writer because of enlarged cervical glands, which proved to be tuberculous. From physical signs a diagnosis of enlarged bronchial glands, involvement of the right upper lobe, and thickened pleura or effusion at the right base was made. The Roentgen-ray picture taken a few weeks later showed extensive disease at the right

root. All the time the child was under observation, whispered bronchophony was present in the interscapular space and was always most marked to the left of the thoracic vertebrae. The child died six months after coming under observation and at necropsy this area was found to be directly over an enlarged gland between the left lobes.

Stoll summarizes his views regarding D'Espine's sign as follows: Whispered bronchophony in the interscapular space is indicative of a pathologic process at the hilus of the lung. This may be due to enlarged glands, the result of malignancy, leukemia, Hodgkin's disease, syphilis, or any infectious disease of the lungs. Its presence in the delicate child is exceedingly suspicious of tuberculous involvement of the tracheobronchial glands.

Occasionally enlargement of the bronchial glands is present when there is no change in the whispered voice. The diagnosis of clinical tuberculosis, however, rests on the sum total of our physical signs and symptoms, not on one isolated sign.

S. Maggiore,⁶⁶ on examining thirty-seven children who gave a positive tuberculin reaction, found an area of dulness in the supraspinous and infraspinoous fossae, in twenty-two instances on the right side, and in fifteen on the left. In twenty-eight, there existed more or less marked evidence of tracheobronchial adenopathy. Radioscopy showed in only four instances any shadow in the upper pulmonary lobes, and in these four cases moist sounds were heard on auscultation. In the remainder, radioscopy gave evidence of enlarged peribronchial glands on the same side as the dulness. There was a necropsy in four cases. In one, in which moist sounds had been present, the lung was healthy, but there were enlarged caseous glands in the region corresponding to the dulness. The conclusion arrived at by the author is that apical dulness in children who react to tuberculin is due, in the majority of cases, to tracheobronchial adenopathy, even when moist râles are present.

T. Gött⁷⁰ describes two cases in which he found an unusual shadow in the roentgenologic picture. The shadow was very similar to the one ascribed by Rach to abscess following a tuberculous spondylitis of the lower cervical or upper thoracic vertebrae. Rach's shadow was bow shaped and extended laterally, in the thoracic region, beyond the shadow of the vertebral column.

Gött's first patient was a 5-year-old girl who had developed a widespread pulmonary tuberculosis following a pneumonia and empyema. Examination on the child's entrance to the hospital showed besides the pulmonary findings, a rigidity of both legs, with increased patella and achilles reflexes, which suggested to the writer incipient meningitis. The Roentgen-ray picture, however, showed shadows which were evi-

dently those of a pulmonary tuberculosis, as well as a spindle shaped shadow, beginning somewhat higher than the bifurcation of the trachea and reaching to the diaphragm. It extended only slightly to the right of the spinal column, but decidedly to the left, so, although it did not conform strictly to Rach's shadow, a diagnosis of spondylitis of the lower cervical or upper dorsal vertebrae was made — especially in view of the rigidity of the lower extremities and the increased reflexes. With this diagnosis in mind the formation of a gibbus and a psoas abscess was predicted, but the diagnosis had to be changed, as six months later there was no evidence of either condition and the rigidity of the legs had disappeared. The Roentgen-ray picture still showed the abnormal shadow and in consideration of the necropsy in the second case, which proved that such a shadow could be caused by enlarged or broken down glands in the posterior mediastinum, the diagnosis of abscess from broken down tuberculous glands was made.

The author's second case was that of a 2-year-old boy, who entered the hospital with symptoms characteristic of a leukemia. The Roentgen-ray picture showed a thick shadow which began at the sternoclavicular joint and ran parallel to the vertebral column. Its median portions merged with the shadow of the vertebral column; its lateral borders were sharply defined and extended beyond the shadow of the vertebral column. Necropsy revealed a leukemic infiltration in the posterior mediastinum near the vertebral column, extending to the level of the tenth thoracic vertebra, which had evidently caused the shadow in the Roentgen-ray picture.

The localization of the pathologic conditions explains the similarity of the Roentgen-ray pictures of two very different processes, and also the similarity to Rach's shadow of spondylitic abscess, which differed from these only in contour.

Pesch⁷¹ reports an instance of rupture of a tracheobronchial gland into the trachea. The patient, a 6-year-old child, was brought into the clinic because of difficulty in breathing. He had been treated about a year for tuberculosis of the knee joint, and he had been coughing a few days. On examining the child there were noted a marked dyspnea, cyanosis and a stridor. During the examination the dyspnea became so severe that tracheotomy was performed immediately, but the child received no relief. Then a forceps was introduced into the trachea through the wound and a small cheesy mass removed from the lower part of the trachea. The breathing became free immediately. The next day, however, the dyspnea and cyanosis returned and were again relieved by removal of another piece of glandular tissue. On the third day several more pieces were coughed up. The child died on the third day.

Necropsy showed miliary tuberculosis of all the organs, caseation of the bronchial and tracheal glands, one of which had perforated the lower portion of the trachea.

The author points out that whenever the diagnosis of perforation seems probable, tracheotomy should be performed and an attempt made to remove the caseated gland through the tracheotomy wound.

A. Wersen⁷² has made some interesting observations — roentgenologic and clinical — on the treatment with calcium salts of bronchial gland tuberculosis. He says that in childhood the bronchial glands are the starting point of most of the tuberculous processes. The bronchial glands enlarge, the lymphoid tissues become necrotic, the capsule thickened and adherent to the surrounding tissues. If the capsule remains intact the tuberculous process heals (usually by calcification) otherwise it spreads rapidly into the lungs, or breaks into the blood vessels. A rational therapy must have, then, for its object a rapid cure of the process, while the capsule of the glands is still intact. For a long time it has been believed that in tuberculosis there is a marked loss of calcium and that this demineralization predisposes to the disease. It has also been thought that calcification is due to the formation of organic substances with increased affinity for calcium. The caseous necrotic masses in tuberculosis of the bronchial glands seem to have this affinity. The question is, can an increased calcium intake influence this affinity and hasten the calcification of the glands? The author has attempted to solve this problem by administering calcium to children suffering from tuberculous bronchial glands and by noting the possible changes, in a series of Roentgen-ray pictures.

Twenty children from 5 to 14 years of age were treated with calcium, nine with calcium lactate, eleven with calcium lactate and sodium tartrate, and the effects on the glands carefully noted in Roentgen-ray pictures. For comparison twenty children not treated with calcium were also observed.

In the first group calcification of the bronchial nodes was noted in eight or perhaps twelve of the patients, in the second series in one, perhaps two, patients. In the first series it was also evident that the hilus shadow became more distinct and more sharply defined from the neighboring tissues, in twelve, perhaps fourteen patients, and in only two of the patients in the second series. Also the clinical symptoms of the patients given calcium were favorably influenced.

On the whole the author is well impressed with the results of this treatment.

PROPHYLAXIS

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A. F. Hess¹⁴ says that in the field of the mode of transmitting tuberculosis the clearer conception as to the time of life when infection takes place — early childhood — is the greatest achievement of the last few years. He raises the question whether this knowledge is profited by in establishing prophylactic measures against the disease. Making investigation in 120 families in which some member suffered from tuberculosis, he found among them forty-two infants under 2 years of age. These children are doomed to contract the disease and to disseminate it. Unless infection in young children is adequately guarded against, there is little hope of eradicating tuberculosis in succeeding generations.

As a remedy, Hess suggests the establishment of preventoriums for infants. To make a beginning in this direction, it may be advisable to assign wards for this purpose in existing institutions (infant asylums, preventoriums or sanitariums) rather than to establish new institutions. It would then be feasible to have in many instances infant and parent in the same institution. These infants need not be sent to the country to undergo a rigorous fresh air regime; they can be adequately cared for in or near the city, where their parents may visit them from time to time. Preference might be given at the outset to urgent cases, to infants surrounded by open tuberculosis, to cases in which a tuberculous mother is constrained to remain at home in order to care for her infant, or in which there are two or more members of the family suffering from tuberculosis. The minimum length of stay may provisionally be fixed at one or two years.

The object, however, of Hess' paper is not to formulate details of such a plan but to urge those engaged in tuberculosis and infant welfare work to make some provision for the large number of infants, who are now abandoned to their fate, destined to die, or to swell the ranks of the tuberculous poor in the coming generation.

Mary E. Lapham⁷⁸ gives some practical suggestions as to the prevention of tuberculosis. She says it is every day becoming more evident that by the time our children reach maturity they are all infected with tuberculosis, that therefore the attempt to protect our people against tuberculosis should be directed not so much against preventing an infection already and inevitably acquired, as toward protection from the consequence of what has already occurred and can no longer be averted. The terrible death rate from tuberculosis is not due to the presence of infection alone, but to the impossibility of knowing when the infection becomes dangerous.

Lapham quotes Allport, who says that there are twenty million schoolchildren in the United States and that one million have tuberculosis. In the present state of our knowledge, then, she says, it is useless to protect our children against this wholesale infection, because we do not know when or how it is acquired. All children are infected and 1 or 2 per cent. will die. The prevention of tuberculosis consists in saving the 1 or 2 per cent., by detecting the infection at the very start, and this can best be accomplished through regular periodic examination of children and adults by competent authorities.

New York City recently advised the yearly examination of each child in the public schools. If this were done by competent authorities, Lapham thinks we might learn that a surprising number of children suffering from tuberculosis regain their lost immunity through the help of open air schools and good food. Also that after a while we may learn that overcoming tuberculosis in the child will stop tuberculosis in the adult.

Lapham mentions the pitiable inadequacy of maintaining sanatoriums at public expense. The number of cases of manifest tuberculosis has not been reduced one whit by sanatorium methods, and can never be reduced by the expenditure of any amount of money, so long as we wait until tuberculosis manifests itself. The yearly examination of every child in the public school, if not ruined by political appointments, will detect when and where tuberculous processes start in the children, and eventually teach us that the danger from tuberculosis is far more from within than from without.

J. H. Peck⁷⁹ emphasizes M. E. Lapham's point that prophylaxis of tuberculosis can best be accomplished by routine examination of schoolchildren for evidence of early signs and symptoms of the disease. In

this way alone can the child be protected from the consequences of the infection.

In an editorial⁷⁷ in the *Archives of Pediatrics* is described the home hospital experiment of the New York Association for Improving the Condition of the Poor. This association wished to ascertain whether it is possible, when one or more in a family are afflicted with tuberculosis, to treat the patients in their own home, without danger to others; whether the results of treatment at home compare favorably with results obtained in sanatoriums, and whether, when tuberculosis and poverty are combined, it costs more to treat the family as a unit than if it is broken up.

The plan of operation has been to place in a sanitary tenement (having sunlight and fresh air in abundance) families selected because one or several members are tuberculous; to keep the family together, using whatever was earned by its members and supplementing this to permit of proper rest, sunlight and fresh air for those who were ill and a decent home for those who were well.

The Home Hospital, located at Seventy-Eighth Street and John Jay Park, occupies two entire sections of the East River Homes. Two open staircases lead to forty-eight apartments, each consisting of from two to four rooms, one or more being bedchambers with open air sleeping balconies. On the roof is a spacious solarium with hedges of privet and geraniums. A part of this solarium is reserved for the patients, another for a children's playground, another for a fresh air school.

The medical treatment has been that of any first rate sanatorium — rest in the open air and extra nourishment, tuberculin in a few cases. Of forty-five adult patients 46.6 per cent. have been cured, 35.5 per cent. have had their disease arrested, 17.7 per cent. have been improved — 99.8 per cent. improved in all. Among the children the improvement was particularly good. Not one unaffected member of any family has shown signs of the disease.

Seventeen families have been rehabilitated physically and their earning capacity restored or even increased; and through the instruction they received they are no longer likely to be a menace to the community, but active centers in spreading a knowledge of hygiene.

Tables of comparative expense show that this method has cost less than any combination of sanatorium and institutional treatment, while it preserves the family unit and its earning capacity.

S. C. Kingsley⁷⁸ describes the open air school movement in Chicago. In the school year 1913-14 there were twenty open air schools in Chicago, with an attendance of over 600 children. The Board of Education furnished teachers and school equipment and the Municipal Tuberculosis Sanatorium of Chicago operated in nursing service and

food. The Elizabeth McCormick Memorial Fund employed special physicians, furnished clothing and gave other necessary service. The children selected were of the undernourished, tuberculous type and came mainly from the congested districts of the city. Seventy-five of the children were tuberculous; 20 per cent. were suffering from anemia and malnutrition; 5 per cent. from bronchitis, heart disease, etc. In addition 188 had diseased tonsils, 165 had adenoids, 466 decayed teeth, 365 defected eyesight.

In order that careful medical work might be done, the Elizabeth McCormick Memorial Fund has paid the physicians of the open air schools, and these physicians have spent an average of four hours a week in each of the nineteen schools. They find it takes a half hour to make a careful examination of each child; and such examinations are made on admission, on discharge and once or twice during the year. In addition, there is a daily supervision of each school. The nursing service takes about an hour and a half a day for each school. The nurse inspects the children daily, supervises the taking of temperatures, visits the homes, and gets the best possible help from the school for the child. Each teacher has only a small number of children in charge, so can know them well.

The children in these schools gain in weight, increase in alertness, in spirit and interest, and make intellectual progress.

C. Dinwiddie⁷⁹ describes the Bamford Hills camp for anemic and pretuberculous children, which is connected with the work of the Cincinnati Antituberculosis League. The camp is situated in a grove near the Miami River. The children are cared for by trained nurses, according to instructions given by the medical director. Their personal habits, diet and recreation are carefully supervised and they are taught the essentials of personal hygiene.

F. S. Minns⁸⁰ describes the method of dealing with tuberculosis in the public schools of Toronto. Medical inspection began there in 1910. At present, the total staff consists of a chief medical officer, twenty medical inspectors, one of whom is a special examiner for tuberculosis, one chief dental officer, thirteen dental surgeons, one superintendent of nurses and thirty-five nurses. All known cases of tuberculosis are recorded and every child suspected of having the disease, or of having been exposed to it, is examined by the special medical examiner. The medical inspectors and nurses assist the special examiner by referring to him all children exposed to, or suspected of having the disease, and by making a report of the home conditions. A record of every child examined for tuberculous infection is kept in the office of the chief medical officer.

Examinations made in the schools are arranged for by the school nurse, who obtains the parents' written consent to the examination.

The work of the department is carried on in conjunction with the work of the family physician, dentist, chest clinics at the hospital, the various missions, the social service organizations and the board of health.

Children examined are placed in one of three groups—those with positive, those with negative and those with doubtful evidence of tuberculosis. Those in the doubtful group are kept under observation and reexamined until placed in either the first or second group. The positive cases are subdivided into two groups, the open and the closed cases. Children who give a positive tuberculin reaction and show clinical evidence of tuberculosis are designated as closed cases. Any of these children who show defects, such as sore eyes, bad teeth, enlarged glands, etc., are referred to the family physician, or to proper authorities for treatment. Where tuberculin treatment is advised, it is given by the family physician or at the Hospital for Sick Children. A large number of the children with closed tuberculosis are sent to a preventorium for one to four months. During the summer, the Board of Education maintains two forest schools for children with closed tuberculosis.

Children with open tuberculosis are excluded from the schools and are visited by the Board of Health nurses. In some instances they are referred to the hospital.

A. Maggiora⁵¹ outlines his ideas as to what the school should do in the combat against tuberculosis. He thinks it the duty of school authorities to conserve the health of its pupils, to build up the delicate ones, to diminish in them the disposition to disease and to propagate the idea that all members of society should contribute to the defense against tuberculosis.

The schools can do this by the following means: A competent physician should examine all children on admission and should make repeated examinations during the school year, in order to exclude any child with open tuberculosis. He should examine the entire personnel of the school for this disease. A separate department, preferably with open air class rooms, should be operated for delicate children. Convalescents from the acute infectious diseases and brothers and sisters of children suffering from the acute infectious diseases should be excluded from school. The locality of the school building, its construction and equipment should answer modern hygienic requirements. The cleanliness of the school should be minutely supervised. The curriculum should be arranged not to overtax the strength of the pupils and athletics should play an important part. A refectory should be conducted, especially in winter, and special nourishment should be provided for the delicate children.

In all schools there should be instituted propaganda against tuberculosis, and all teachers given instruction in hygiene.

Thiele-Chemnitz⁸² deplores the law which excludes tuberculous children from school without making other provision for their education. He quotes Kirchner, who says that to forbid a child to attend school is to close the future to him. Tuberculous children should be placed where they cannot harm others, yet they should not be deprived of means of development.

The ideal is a sanatorium and school combined, in which the curriculum is arranged not to overtax the child.

A. Wallgren⁸⁴ emphasizes the importance of exposure to tuberculosis in the family during childhood. Among 100 tuberculous persons, he found in 51 per cent. a history of exposure to tuberculosis in the family before the age of 15; among 100 nontuberculous persons, in only 13 per cent. A history of exposure before the child was 5 years old was ascertained in 15 per cent. of the tuberculous and only 1 per cent. of the healthy children. Among the 100 tuberculous persons, one or both parents in 27 per cent. had been tuberculous; a brother or sister in 6 per cent., and other relatives in 11 per cent. Among the 100 healthy persons, only 2 per cent. had a history of tuberculous parents; 2 per cent. had a tuberculous brother or sister, and 2 per cent. other tuberculous relatives.

Thiele⁸⁵ compared the height and weight of 1,000 normal school children with that of 300 tuberculous children. He found that on entrance to school, tuberculous boys and girls weighed less than the normal children, and that the boys were also somewhat smaller, and manifested a marked retardation in weight and height throughout the entire school time. In the girls the failure to gain sufficiently in weight and height lasted until the middle of their school time. Then there was a rapid gain in height without a corresponding gain in weight. This gave rise to the "phthisical habitus" which, as is well known, appears later in boys than in girls.

Tuberculosis then has a detrimental effect on the development of the child, a fact to which too little attention has been paid.

W. L. Moss⁸⁶ has attempted to immunize calves against tuberculosis by feeding them the milk of cows vaccinated against the disease. He says it has been proved that an efficient immunity is established against a number of infectious and toxic agents; that, in the case of most of these, immune bodies can be demonstrated in the blood; that these immune bodies may appear in the milk also; that from the milk they may be absorbed from the alimentary canal of the infant and appear in the blood, where they exert a definite protective influence. He says, moreover, that active immunity against tuberculosis has been established in cattle, and he quotes v. Bering who has suggested the possibility of conferring passive immunity on infants by giving them the milk of vaccinated cows.

Moss performed two series of experiments. In each six calves of approximately the same age, weight and breed were selected. Three of these calves were from birth fed on fresh mixed milk of several vaccinated cows. The other three calves were fed with milk from unvaccinated cows. To vaccinate the cows, four intravenous injections of a suspension of living human tubercle bacilli were given at intervals of three weeks. After several months a virulent strain of bovine tubercle bacillus was used as a test inoculation. In the first series 1 c.c. of the suspension was inoculated into the anterior jugular vein. After the test all the calves rapidly developed tuberculosis and died during the fourth week. Evidently the dose was excessive and masked any evidence of immunity which might have been present in the calves fed on milk of vaccinated cows.

In the second series, the same dose of virulent tubercle bacilli was given subcutaneously. The three calves receiving milk from the immunized cows thrived better than the other three, and at the time of necropsy weighed 25 per cent. more. A month to six weeks after the injection both groups developed lesions at the site of inoculation. In the calves receiving the milk of immunized cows the lesions were small and difficult to palpate, while in the other group they were very evident. The calves were killed and at necropsy tuberculosis lesions were found to be much more marked in the nonimmunized animals.

The blood of the calves of the two groups was tested for tuberculo-antibodies but no difference could be determined by means of the agglutinin, precipitin or complement binding tests.

The author thinks the conclusion justified by the results of the second series, that a relative degree of immunity against tuberculosis may be conferred on cows by feeding them the milk of vaccinated cows. Further experiments are necessary to determine whether human beings are similarly influenced.

TREATMENT

89. Woodruff, I. O.: The Care of the Tuberculous Child, *Arch. Pediat.*, 1915, *xxxii*, 490.

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94. Richards, G. L.: Relation of Tonsils, Adenoids and Other Conditions to Tuberculous Adenitis, *Boston Med. and Surg. Jour.*, 1915, *clxxii*, 1.

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I. O. Woodruff,⁸⁹ discussing the care of children suffering from tuberculosis in the early stages, finds the necessary preliminary step to

be accurate diagnosis. In this, familiarity with tuberculosis as manifested in the adult is of little value. But when it comes to treatment, important, as with the adult, are rest, fresh air and superalimentation. Rest especially should be emphasized. The orthopedic surgeons have long appreciated the necessity of absolute rest of the affected part in tuberculous bone and joint disease, so long as the process is active, and it is the writer's experience that rest is quite as essential in pulmonary disease. While the temperature in children does not seem to be affected by the toxemia or by exercise, the pulse is particularly susceptible, and it is well to base the amount of exercise in which the child may indulge on its condition. As the child improves more and more exercise can be introduced. In the sanatoriums and camps, a children's garden can be used admirably for this purpose. Exercise must be graduated, the pulse and temperature noted before exercise and one half hour after it, and the work graded according to its effects. Mentally satisfying the child with quiet occupation is important and simplifies the problem of restricted exercise. Schooling, always in the fresh air, may be permitted. Rest in a reclining posture should be insisted on for one hour after the midday meal. When the disease is quiescent or in an apparently arrested stage, postural and breathing exercises exert a marked benefit.

The value of fresh air is well established and the nearer to twenty-four hours a day it can be had, the better. It is fresh air rather than the air of any particular locality which is valuable, though an equable climate with fairly cool temperature, no dust or high winds is most satisfactory. A particular bad combination is heat and humidity.

As to diet, foods of high caloric value are indicated, until the weight is normal or slightly above. The type of diet is one high in protein and fat. Digestive disturbances are less likely to occur, if superalimentation is brought about slowly.

Of the adjuvants to rest, fresh air, and feeding, Woodruff mentions tuberculin. He uses it only for those patients who do not improve under ordinary remedial measures. He employs old tuberculin in very small doses. In cervical gland tuberculosis the writer is distinctly enthusiastic over the use of tuberculin. Surgical measures are indicated only where caseation exists or where the glands are present in large numbers.

A tuberculous child may be permitted to resume normal life when the pulmonary signs have entirely disappeared or have remained stationary or inactive for a period of months; when nutrition is normal; when the pulse is of normal rate and range and of good stability.

Woodruff lays especial stress on the after care of the child who has had an active tuberculosis, and on the prophylaxis of the disease. The fresh air class, he says, is the best avenue by which a child may

return to normal life. A child cured of the disease should sleep constantly with the window open or, if practical, out of doors. Each child should be discharged on probation, and at first should report once a month for examination. Later the period can be lengthened.

As a phase of after care, attention should be paid to the condition of general nutrition and chest development. Periods of rapid growth should be carefully watched. Whooping cough and measles should be guarded against.

In regard to prophylactic measures, Woodruff quotes figures showing that bovine tuberculosis is a menace important enough to be seriously considered. Raw milk can be relied on only when obtained from certified herds under proper supervision. Where standards of supervision do not prevail the public must be impressed with the necessity of pasteurizing the milk, or, better still, if its use is temporary, of boiling it, when intended for children.

The prevention of infection from human sources presents many problems. Too intimate contact with the infected member of the family must be prevented. Young children who creep or play on the floor must be excluded from the patient's rooms; carpets must be abolished; dustless methods of cleaning must be employed; washable rugs or rugs covered with muslin used. In municipal work, preventive measures include the iteration and reiteration of the necessary of care; the provision of a separate sleeping room for the adult patient, and the removal of the patient, if necessary, from the family; the sending of children at intervals to preventorium.

If infection has taken place, the problem is to prevent its extension and development. This includes improving the state of nutrition, correcting defective posture and developing the chest by appropriate exercise; correcting of various physical defects, especially dental caries, hypertrophied tonsils and adenoids. All exposed children should have a cutaneous test. Children who do not react should be tested every four or six months. Children under 3 or 4 years who react to tuberculin are in need of medical care and are especially suitable for preventorium treatment.

H. Koch⁹⁰ has given tuberculin rather extensively in the treatment of tuberculosis in children and believes success depends on the technic of its administration. He reports his experience in the treatment of forty-five cases. He used only two preparations, Koch's old tuberculin and the albumin-free tuberculin. The initial dose was $\frac{1}{1000}$ mg. of old tuberculin and $\frac{10}{1000}$ mg. of the albumin-free tuberculin. This dose was increased in geometric progression, until doses of 1,000 mg. of old tuberculin and 10,000 mg. of albumin-free tuberculin were reached. The number of doses between the initial and final doses were seven (rapid increase) thirteen (medium) or twenty-five (slow). On an

average, however, the end-dose was reached by eighteen injections or in nine weeks, as two injections were given each week. The cause of this was a necessity of repetition of the same does or the return to a smaller dose, on the one hand, and the skipping to a larger dose, on the other. In the writer's cases delays due to repetition of doses were comparatively rare. The end-dose was repeated in a number of instances.

Both preparations of tuberculin were given well diluted with physiologic salt solution (10 to 20 cm.). This large amount of fluid seems to aid absorption and allows of a general distribution of tuberculin throughout the body and a general formation of antibodies.

The injections were given between the shoulder blades and never twice in the same place. In this way reactions were avoided. Reactions from injections of tuberculin may be general or local. Of the general reactions the most important was fever. In nineteen of the cases there was undoubtedly a febrile reaction. It occurred eleven times with normal increase of dose, five times after repetition of the dose and five times with a rapid increase of the dose.

Inflammatory manifestations at the site of injection occurred in seventeen cases: in eight cases once, in six cases twice, in two cases three times and in one after every injection. This last case was not suitable for tuberculin treatment.

In seven cases the tuberculin cure was interrupted. In three of these there was a wide-spread infiltration of the lung with cavity formation; in two cases, one of scrofula and one of tuberculosis of the skin, the local reaction was too severe to continue and in two cases of multiple tuberculosis of the glands the course was not influenced.

Good results were obtained in the other thirty-eight children. Their general condition improved, the fever either disappeared or was less severe and the tuberculous process was favorably influenced. In two cases of pulmonary tuberculosis there was retrogression of inflammatory manifestations, the tubercle bacilli disappeared from the sputum and there was a partial cessation of cough.

Only a few forms of tuberculosis in children are not suitable for specific treatment. To these belong severe phthisical processes, amyloid degeneration of the parenchymatous organs, cases with marked reactions to tuberculin, cases of miliary tuberculosis and of tuberculous meningitis.

The good results which Koch has obtained with tuberculin makes him recommend its use in tuberculosis of childhood.

In spite of the fact that experimentally J. Bacigalupo²² could not be convinced of the penetrability of various substances into the serous cavities under normal and inflammatory conditions, he determined to

try the effect of intradural injections of tuberculin in cases of tuberculous meningitis.

The first case was one of advanced tuberculous meningitis, complicated by miliary tuberculosis. Twenty-four hours after the injection there was some amelioration of the brain symptoms, but the child died three days later. Bacigalupo gave the same treatment in two uncomplicated cases, in both of which tubercle bacilli were found in the spinal fluid. In both the results were very satisfactory, and there was complete recovery after two or three injections in the course of twenty days. Worthy of note is the fact that there was no reaction to the tuberculin in any of the three cases.

As regards dosage, in all three cases the first dose was 1 mg. followed by a somewhat larger dose in twenty-four hours, if there was no improvement in symptoms.

As the author finds only twenty-two recoveries from tuberculous meningitis reported in the literature, he thinks it is worth while to try further intradural injections of tuberculin.

H. D. Chadwick⁹³ describes a method of treating children admitted to the Westfield Tuberculosis Sanitarium. Most of these have tuberculous cervical glands and also enlarged bronchial glands, as evidenced by impaired resonance between the scapulae. Chadwick puts these patients on bacillen emulsion, if they do not have more than a degree of fever or show signs of active pulmonary disease. The initial dose is one-millionth of a milligram and is increased in the course of six months until the maximum 10 mg. is reached. This maximum could be reached in a shorter time, but a small dose given over a longer period is more effective and does not cause reactions.

The results of treatment in these children is very satisfactory. The cervical glands decrease in size and the area of dulness over the hilus becomes smaller. Suppuration never occurred, when it had not existed before treatment. This experience leads the author to the conclusion that surgical interference is necessary only to remove such glands as have become caseous or fibroid.

G. L. Richards⁹⁴ discusses the relation of tonsils and adenoids to tuberculous cervical adenitis. There are two principal retropharyngeal glands, one on either side of the median raphé. These glands receive lymph from the mucous membrane of the nasal fossae and adjacent cavities and drain into the upper glands of the internal jugular chain. The general lymphatic drainage of the pharynx also ends in the retropharyngeal glands and the internal jugular chain. The glands of the internal jugular chain receive also the lymph from the internal group of the sternomastoid glands.

The lymphatics from the tonsil drain into the lymph glands of the tongue, thence into the two lateral trunks, which pass down the

lateral wall of the pharynx and terminate in the large glands of the internal jugular chain. A not inconsiderable number of lymph vessels go directly from the posterior pharyngeal wall to the deep glands of the neck and internal jugular region.

The adenoid area drains into the posterior wall of the pharynx. The lymphatics of the larynx drain into the glands of the internal jugular chain.

Richards thinks that after the removal of the faucial tonsils in children suffering from enlarged cervical glands, these glands disappear and are no longer palpable. He recommends in all cases of cervical adenitis that the tonsil be removed as the first procedure, but he does not assert that the removal of the tonsils removes all danger of infection of the cervical lymph glands, since the anatomic studies referred to show that the area of the middle ear, Eustachian tube, superior, posterior and lateral pharyngeal wall, the tonsils, base of the tongue, and posterior nares, all drain into the cervical lymph glands.

L. B. Meyer⁹⁵ believes in the conservative treatment of tuberculous cervical glands and he particularly emphasizes the importance of correcting in the mouth and nasopharynx all pathologic conditions which might act as a source of infection. Diseased tonsils and adenoids should be removed and the proper treatment for decayed teeth be instituted. This accomplished and the various hygienic and tonic measures recommended for tuberculosis carried out, a large majority of patients with tuberculous glands will probably never need surgical treatment. If, however, the glands do not disappear under this régime, they often will if treatment is directly applied to them. Of these Meyer mentions injection of 5 per cent. iodoform emulsion in oil, or 2 to 4 per cent. formaldehyd solution in glycerin, the use of Biers hyperemia, of tuberculin, and Roentgen ray.

If the patient is not seen until a glandular abscess is formed or a sinus exists, treatment must be directed to prevent the formation of disfiguring scars. Often appropriate treatment applied to throat and mouth is followed by retrogression of the glands and healing of the sinus. If not, a little assistance with a curet or stimulation with tincture of iodine, or the use of Beck's paste is all that is needed. If an abscess exists, the pus must be evacuated either by aspiration or with a narrow knife. It is usually better to wait, in this condition, for complete caseation of the gland.

Meyer cautions against extensive dissection in these cases.

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OBSERVATIONS ON 100 CASES OF THE INFANTILE TYPE OF HEREDITARY SYPHILIS *

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As a part of a general investigation of hereditary syphilis, 100 consecutive cases of the infantile type were tabulated for special study. Some points were brought out in this way on which little stress is placed in the usual textbook discussion of hereditary syphilis, and it has seemed of sufficient value to put some of the results of the study on record.

From a clinical standpoint we divide hereditary syphilis into fetal, infantile, late or tardy, and latent types. The term infantile we limit to those cases in which the signs develop after birth and during the first year of life. Although the infection in all types takes place *in utero*, we limit the term fetal syphilis to those infants in whom manifest signs of lues are present at the time of birth; thus it includes abortions, stillbirths, and both premature and full term living infants. Late syphilis was discussed in an earlier paper¹ and we designate as latent, those apparently healthy children of syphilitic parentage who show no symptoms except a positive Wassermann reaction (WR). In this paper we have limited the discussion to 100 consecutive cases of the infantile type observed in the St. Louis Children's Hospital and the Pediatric Clinic of the Washington University Medical School.

An attempt has been made to follow up and keep in touch with every case of syphilis for the past three years, but false addresses, lack of cooperation on the part of parents and the impossibility of making some parents realize that a child in whom all active signs have disappeared is not "cured," have greatly hindered the effectiveness of this work. We have been able, however, to keep in touch for many months with a large part of the cases, and but a few are recorded as having made but one visit to the dispensary. We have even gone so far in some cases as to invoke court aid in forcing parents to have

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1. Veeder and Jeans: The Diagnosis and Treatment of Late Hereditary Syphilis, *AM. JOUR. DIS. CHILD.*, 1914, xii, 873.

a syphilitic child treated, although this has usually resulted in the treatment being outlined and supervised by other clinics or private physicians.

SYMPTOMATOLOGY

In taking histories certain symptoms were carefully inquired into, and these were again noted in the physical examination. As the cutaneous eruptions and the rhinitis or coryza are the most striking lesions objectively, and as they furnish as a rule the complaint for which the infant is brought to the physician, they are the most important of the symptoms. Epiphysitis—or more correctly “Parrot’s pseudoparalysis”—while less common, always serves as a chief complaint when present. The spleen is the most important guide to visceral lesions, as it is not normally palpable. An enlargement of the liver is more difficult to classify as an abnormal physical sign, although histologic changes are more common in this organ. The state of the infant’s nutrition is also an important factor—to some extent in the symptomatology but more so from the standpoint of prognosis. These symptoms, together with the time of appearance of the first manifestations of the luetic infection, have been considered in detail.

Cutaneous Lesions.—A syphilitic rash or a cutaneous lesion of some type was present in 77 cases and absent in 23. Although a number of types of eruption are described by dermatologists as occurring in infants with hereditary syphilis, the cases in our series fell almost entirely into two simple types which were occasionally combined. We have considered in this respect but 64 cases in which the skin lesion was actually seen by us. A macular, or slightly maculopapular rash occurred in 14 cases, while in 48 the eruption was confined largely to an exfoliative or desquamative dermatitis involving the soles of the feet and the palms of the hands. The skin beneath the scaling epiderm is glistening and shiny. We have never seen this type of lesion in an infant unassociated with syphilis, and in our experience it is the most characteristic form the hereditary syphilitic eruption assumes, although not generally so considered. Certain individual cases showed some interesting features in regard to the skin lesion. One infant was brought to the clinic when 3 months old with a rhinitis, at which time the WR was positive. After a few weeks the parents refused to continue treatment and at 10 months the child was again brought for treatment because of the development of a maculopapular syphilid. In this case there was an interval of seven months between the development of the rhinitis and the rash. In three cases the cutaneous lesion was in the form of condylomata. These developed late—tenth to twelfth month—and in two of the cases there had been no earlier skin

involvement, although in the third case there was a history of an eruption at 2 months. Another infant, admitted to the hospital for malnutrition, was found to have ulcers of the groin: The WR was positive and the lesions cleared rapidly under treatment (neosalvarsan). Vulvar ulcerations were noted in one infant a month old. At times small bullae or blebs were present, especially about the moist surfaces, or there was a slight secondary infection, but neither a true bullous dermatitis or pemphigoid eruption, nor a typical pustular syphilid was observed in any of the cases in our series.

Rhinitis.—This was present to a greater or less degree in 74 cases and was noted as absent in 26—an incidence almost the same as that of the rash, although they by no means were always associated in the same case. Thus a 9-weeks'-old infant admitted to the hospital for malnutrition developed a syphilitic rash while under direct observation, but at no time was a rhinitis present. The rhinitis was more apt to be present in the cases developing early in infancy and likewise was one of the first symptoms to disappear under treatment.

Spleen.—In 82 cases the spleen was definitely palpable while in 18 it could not be felt on physical examination. These negative cases occurred in both the young and older infants. In 3 cases—all over 8 months—an enlarged spleen, together with wasting were the only signs of syphilis present in addition to a positive WR. These are borderline cases between the clinical division into latent and infantile syphilis. We feel it is better to recognize malnutrition as a symptom of the infantile type of hereditary syphilis and limit the term latent to apparently healthy infants and children. In our clinic an enlarged spleen in an infant under 6 months without symptoms of an exudative diathesis has usually proved to be indicative of syphilis or tuberculosis, and hence a WR test is made in addition to the routine tuberculin test which each infant receives. The rachitic spleen is later in development and other causes, such as occasional malarial spleen or a splenic tumor, are uncommon.

Epiphysitis.—This was present in 14 cases and absent in 86. In 8 of the 14 cases the epiphysitis developed between the fourth and sixth week. The earliest the lesion was noted was at 2 weeks and in two cases it did not develop until the third month. What we mean by epiphysitis in this connection is really the so-called "Parrot's pseudo-paralysis" of hereditary syphilis. Necropsy examination as well as roentgenograms show an epiphyseal lesion to be very common in hereditary syphilis. It is only when the epiphysitis extends to and involves the periosteum and muscles that a lesion which is recognizable clinically is produced, and which is commonly spoken of as epiphysitis.

Nutrition.—It is generally accepted that syphilitic infection acts in two ways on the infant. First, by producing specific lesions such as those described above, and secondly, by acting deleteriously on the nutrition and development of the infant as a whole. This malnutrition has been very striking in connection with the infants in our series, and in order to show this we have averaged the weights of the infants at the time of the first examination, as the weight is the most satisfactory index of the condition of nutrition. Of 77 infants whose weight was recorded in the histories, 7 were overweight, 10 of average weight and 60 below average weight. The extremes were from 1,430 gm. overweight, to 3,100 gm. under weight. The 77 infants averaged 1,480 gm., or little more than 3 pounds below the average weight of a like number of infants of the same ages. This condition of malnutrition is not only one of the most constant and striking symptoms of the luetic infection, but it is also one of the most important factors in the production of the high mortality rate of hereditary syphilis, which is discussed below with the question of prognosis.

TIME DEVELOPMENT OF THE EARLIEST SYMPTOMS

In Table 1 we have recorded the time of the appearance of the first manifestations of the luetic infection as they appeared in ninety-five of the cases. In a few cases the facts were too indefinite to be included.

TABLE 1.—TIME OF DEVELOPMENT OF EARLIEST SYMPTOMS

Time of Appearance	Cutaneous Eruptions	Rhinitis	Epiphysitis	Wasting and Wassermann Reaction	Jaundice	Hemorrhage and Edema	Total	
1 week.....	4	12	16	Total in first month, 51
2 weeks.....	2	3	5	
3 weeks.....	3	6	5	14	
4 weeks.....	7	6	2	1	16	
5 weeks.....	..	1	1	2	Total in second month, 30
6 weeks.....	6	7	13	
7 weeks.....	2	3	5	
8 weeks.....	6	1	1	1	1	..	10	
3 months.....	5	1	6	Total in third month, 10
4 months.....	1	1	..	3	..	Iritis 1	6	
6 months.....	1	1	
10 months.....	1	1	
Total.....	38	41	9	4	1	2	95	

It will be noted that 81, or 85 per cent., of the infants developed symptoms in the first two months of life and about two thirds of these within the first month. The development of symptoms was delayed until late in infancy in a few cases. Thus, one infant first examined at the age of one month and subsequently under constant supervision did not develop signs of lues until the fourth month, when a typical cutaneous eruption appeared and the WR was positive. A rhinitis was the most frequent "earliest symptom" to develop and this was especially so in young infants. Although the rash at times appeared early, there was a tendency for it to be later in development than the rhinitis, in so far as first symptoms are concerned. The other primary symptoms are of too infrequent occurrence to be discussed in detail.

WASSERMANN REACTIONS

The Wassermann reaction was made in 82 cases. The results were as follows:

Positive	76 or 92.6 per cent.
Doubtful	1 or 1.3 per cent.
Negative	5 or 6.1 per cent.

In eighteen cases no test was made for various reasons—usually because of very small babies with active signs whose mothers gave a + WR. The percentage of positive reactions, 92.6, is about the same as that usually quoted for the incidence of a positive WR in cases of hereditary syphilis. In an earlier study of the "late" type we found a positive WR in all of a series of 73 cases, or an incidence of 100 per cent. Including these two series we have treated some 300 children with hereditary syphilis in the past 3½ years and in nearly 98 per cent. of these the WR has been positive. One of us² found that in a series of 86 mothers of syphilitic children, 73, or 85 per cent., had a + WR—a figure close to that for the + WR in these infantile cases.

It has been found that occasionally very young infants with clinically undoubted syphilis fail to react positively to the WR. Most of these negative findings have been in the first few weeks of life. In this connection our five negative cases are interesting as they do not all come under this class. The data for each is briefly as follows:

1. Treated at 3 weeks. Clinically positive; syphilis in both parents; died before a second test could be made.
2. Tested at 3 weeks. Typical eruption; positive Wassermann in rest of family; given treatment and Wassermann again negative at 8 and 17 months; no late symptoms have developed as yet.
3. Tested at 3 months. Typical eruption and enlarged spleen; Herxheimer reaction following injection of neosalvarsan.
4. Treated in 3 months. Rhinitis; typical eruption; enlarged spleen; Wassermann in both parents positive.
5. Treated at 5 months. Rhinitis; typical eruption; enlarged spleen.

2. Jeans, P. C.: Familial Syphilis, *AM. JOUR. DIS. CHILD.*, 1916, xi, 11.

The last three cases can hardly be placed in the above mentioned well recognized group of clinical infantile syphilis giving a negative WR. It would hardly seem that the usual explanation for these negative reactions—infection late in pregnancy with lack of sufficient time for the formation of antibodies—can be offered for the last three cases, and we can only say that for some unexplained reason there was a failure in these cases of the formation of reactive bodies. None of the three infants had received treatment before the WR was tested. We must recognize that while a negative WR is extremely rare in the late type of syphilis (we have met with but one questionable case), it occasionally occurs in the infantile type.

PROGNOSIS

The prognosis of an hereditary syphilitic infection is bad. In another paper one of us² has shown that of 331 pregnancies occurring in 100 syphilitic families, 131 terminated in death before term, and of the 200 living births, 51 children had died. Another study³ bearing on this fact compared the total pregnancies occurring in 100 families with contagious disease, 100 taken at random from our records and 83 families in which there was syphilis. The total waste as obtained by taking the total number of living children in relation to the total pregnancies was 25 per cent. for the first two groups and 46 per cent. for the syphilitic group.

It is extremely difficult to get exact figures for the death rate in a series of consecutive cases such as form the basis of this paper, when the infants have to be followed for a long period of time and where the condition under discussion is not acute. Even in countries in which the registration of the population is rigidly enforced this is not an easy task. Thus Welde⁴ in Berlin lost track of 32 of 100 polyclinic cases. With the aid of an active social service department and a rather laborious explanation to the parents of each child of what the disease portended, we have been able to keep in touch with nearly all of our infantile cases for periods of many months. The deaths, as will be seen from the figures given below, practically all occur in the first few months and as a general rule infants over 10 months do not die of the syphilis itself. We have found it necessary, therefore, to divide our cases from the standpoint of mortality into three groups:

1. Known dead.....	28
2. Alive and over 10 months of age. (Some now over 3 years.)..	28
3. Infants under 10 months, when last seen.....	44

3. Jeans and Butler: Hereditary Syphilis as a Social Problem, *AM. JOUR. DIS. CHILD.*, 1914, viii, 327.

4. Welde: *Ergeb. d. inn. Med. u. Kinderh.*, 1914, xiii, 405.

As to this last group of 44 cases, twenty were lost track of at some period between the second and tenth month and twenty-four are now under observation. Some are in wretched condition and the prognosis is absolutely hopeless; likewise some of those lost from view undoubtedly died. We can confidently say that in at least twelve of these cases the prognosis offers no chance for life, and this figure will more likely reach 15. If these 12 are added to the 28 known deaths in the series the mortality figure for the series reaches 40 per cent., and this despite the fact that many of these infants have been treated intensively with both neosalvarsan and mercury. This figure is but little less than that of Heine,⁵ who reported 45 deaths in a series of 100 syphilitic infants in Berlin. In Table 2 the age of the infant at the time of death is shown for the 28 cases.

TABLE 2.—AGE OF INFANT AT TIME OF DEATH IN TWENTY-EIGHT CASES

Age, Months	No. of Deaths	Age, Months	No. of Deaths
1	4	6	3
2	5	7	1
3	4	8	1
4	4	9	1
5	4	10	1

It will be noted that the deaths are almost entirely confined to the first half year of life.

It has been surprising to us to find that treatment, *per se*, seems to have but little effect on the immediate outcome of the case. This was a clinical impression which we have found supported by our statistics. We have seen case after case cleared of all syphilitic manifestations as a result of treatment, gradually waste away and die of malnutrition. Even at necropsy no distinctive syphilitic changes have been found in some of these cases and the tissues have been negative when examined for spirochetes. Again, other infants with little or no treatment develop into robust and apparently healthy children. The one factor of greatest importance is the condition of the infant's nutrition. As we have pointed out above, this is impaired in such a degree of frequency and to such an extent that the malnutrition may be regarded as a symptom. As nutrition is to such a large extent dependent on the diet, we have tabulated the relationship existing between the infant's diet and the mortality. We have classified 87 cases, from the standpoint of the food

5. Heine: Prognose u. Symptomatologie d. heredeterie Lues im Säuglingsalter. Jahrb. f. Kinderh., 1910, lxxii, 328.

the infant received into three groups (Table 3). In 13 the record gave insufficient data as regards the diet.

TABLE 3.—RELATIONSHIP BETWEEN DIET AND MORTALITY

	Living	Dead	Bad Prognosis
1. Artificially fed, including babies fed less than 1 month on breast	9	17	8
2. Breast fed up to between 1 and 8 months, then artificially fed	10	6	2
3. Breast fed over 8 months (many of these on breast 6 months)	42	8	5

These figures show clearly the value of breast feeding. The increased death rate of the artificially fed infants with syphilis over that for the breast fed is much higher than the increased rate for artificially fed infants in general. These figures show strikingly what clinical observation has indicated, that the outcome of a case of infantile hereditary syphilis is to a large extent dependent on the condition of the infant's nutrition. While the character of the specific treatment may be of considerable importance in relation to the development of late lesions, the prevention of cerebrospinal syphilis, etc., it is by no means so important as the character of the nutrition as regards immediate life or death. Not infrequently we have seen severe syphilitic lesions disappear with very little treatment and infants in whom symptoms had persisted for a long time make a splendid and rapid recovery, while, on the other hand, infants with what was apparently a mild degree of infection, as manifested by the symptoms, have succumbed after a vigorous and intensive course of treatment. In our experience the prognosis is chiefly dependent on the state of nutrition, and this in the ultimate analysis leads back largely to the manner in which the infant has been fed.

TREATMENT

It is rather difficult to summarize the results of treatment, yet, on the other hand, it is obviously impossible to discuss a large number of individual cases. We have attempted to carry out various methods of treatment and combinations of drugs in a comparative way, being governed to a large extent in methods by the case as an individual problem. In some cases in our series the duration of the treatment was too short to be of any value in forming an opinion as to the efficacy of the method, and in 11 cases no treatment was instituted for various reasons. We have been able, however, to accumulate sufficient data in 73 cases, in 41 of which neosalvarsan was used in combination

with mercury, and in 31 some form, or forms, of mercury alone was given. As experience has shown that neosalvarsan alone is not as efficacious as when combined with mercury, but one infant was treated in this way. We do not use iodids in the treatment of hereditary lues. In the light of the specific action of mercury and arsenic on the comparatively recently-discovered etiologic spirochete of syphilis, it is hardly a rational procedure, and, moreover, it is a drug not easily borne by the infant. The various combinations and the number of cases in which each was used is shown in Table 4.

TABLE 4.—FORM OF TREATMENT AND NUMBER OF CASES

Neosalvarsan	1	
Neosalvarsan with gray powder.....	21	41
Neosalvarsan with inunction.....	8	
Neosalvarsan, gray powder and inunction.....	12	31
Inunctions	13	
Inunctions and gray powder.....	7	
Gray powder	11	

The neosalvarsan injections were all given intravenously by means of a glass syringe into the median or external jugular veins, as a rule. The dosage used was 0.075 to 0.15 gm., according to the size of the infant. No bad results were experienced following the injections. The 42 infants receiving neosalvarsan were injected as follows:

21 cases received 1 injection
 12 cases received 2 injections
 7 cases received 3 injections
 2 cases received 4 injections

The deaths were divided proportionately between the cases receiving mercury alone and mercury in combination with salvarsan. For the reasons discussed above, the mortality is of little service as an index of the value of specific treatment in these cases, and we can only form an opinion by considering the effects of treatment on the symptoms.

Neosalvarsan causes a rapid disappearance of the syphilitic lesions, especially of the cutaneous symptoms and the rhinitis. It is more rapid in its effects than inunctions of mercury, and much more so than gray powder used alone. Intramuscular injections of mercury are not suitable for use in infants or in children. It is a simple procedure to inject neosalvarsan intravenously and we use it freely in the outpatient dispensary without admitting cases to the hospital. The only precaution to be taken is that it must be injected directly into the vein without any of the solution escaping into the perivascular tissues. This requires some degree of skill and practice for small veins and hence the external jugular is easier for routine work. In a number of cases the use of neosalvarsan has caused such a rapid disappearance of the rash and rhinitis that it has been difficult to persuade the parents that the condition was not trivial and that the child required further treatment.

The hardest problem as regards the medicinal treatment of hereditary syphilis consists in persuading the parents to persevere in treatment after the active signs of the infection have disappeared. On the other hand, inunctions are unpleasant and very much objected to by the infant's caretaker as a rule. Nevertheless the treatment should be started by one of these two intensive methods of combating the infection. We find it most satisfactory soon to discontinue the one used and change to gray powder, which is the most useful form of mercury we have found for treatment over long periods of time, as it causes as a rule the least disturbance to digestion. If started early, before all active signs have disappeared under the more intensive inunctions or salvarsan therapy, it is more apt to be continued for a longer period of time. The ideal method for practical purposes, and the method which gives best results, in our experience, is two injections of neosalvarsan with a three-day interval followed by a series of courses of gray powder (gr. 1.5 t.i.d.) of a month or six weeks' duration, with an interval of from ten days to two weeks between courses. These should be continued well into the second year of life or until the WR has been made persistently negative, if the case can be kept under control for such a length of time. If neosalvarsan is not available, a course of inunctions of mercury (gr. 10 to 15 daily) lasting two weeks, may be substituted. It is at times surprising to find how the WR persists after seemingly intensive treatment in many cases. We are trying to ascertain how many of these infantile cases in which the extent of the treatment is known develop "late" lesions in childhood, as we know of no studies in regard to this point, but the nature of the material at our disposal makes such a study difficult. A careful control of the diet and of the general hygiene is as essential as the specific therapy as far as the immediate treatment of the case is concerned.

TREATMENT AND THE WASSERMANN REACTION

In a previous paper we made the statement that we had been unable to obtain a persistently negative WR in a child with "late" hereditary syphilis, despite the most intensive treatment. Although some of the cases reported at that time have been under treatment for a year and a half since, we have no cases as yet which lead us to modify this statement. This, however, does not hold true for the infantile type, as in a number of the cases in this series the WR has become negative as the result of the treatment outlined above and has remained so for many months, nor have these cases developed any further symptoms of lesions of a syphilitic nature. In other words, it seems probable that some cases have been cured, if, as is held at present, a persistently negative WR constitutes a proof of cure. In the majority of

cases, however, it would seem as if the condition had only become latent or quiescent as the result of treatment and only the subsequent course of the case can be determined whether this treatment—which has caused the disappearance of all clinical manifestations, but which has not affected the WR — has been sufficient. From our knowledge of the early treatment of many children with late lesions we are not very optimistic in regard to this group of infants. Cases of apparent clinical similarity respond differently to the same kind and amount of treatment. In some of our cases the WR has become negative, while in others treated in the same way it has remained positive. No general rules, therefore, can be deduced from our cases in regard to the length of time treatment is necessary for the production of a negative WR. Each case in this respect must be treated individually and we can only say that if the development of late lesions is to be inhibited, it is apparently necessary to continue the treatment of an infant with syphilis until the WR has become negative and remained so after an interval of freedom from specific medication.

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LOBAR PNEUMONIA IN CHILDHOOD; ROENTGEN-RAY FINDINGS AND AN EXPLANATION OF BRONCHIAL SIGNS.*

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During the past two years all cases of lobar pneumonia on the Children's Service at the Presbyterian Hospital have been roentgenographed at least once. In those cases showing a shadow, but in which bronchial voice and breathing were not heard, repeated roentgenograms were taken at varying intervals. The purpose of these examinations was to ascertain whether the consolidation as evidenced by this shadow passes through any regular development, and if so, whether the different stages of its progress can be correlated with the development of certain physical signs.

Most textbooks have little to say regarding the site of the early consolidation in lobar pneumonia, or the way it spreads, nor do the books on physical diagnosis correlate the development of the physical signs with the conditions in the chest. When the signs which are considered diagnostic of consolidation appear late or are entirely absent, we find the term "central pneumonia" introduced to explain the unusual situation. Tripier,¹ however, states definitely that the consolidation always touches the periphery of the lung and that the process is most intense at this point. The consolidated area, he says, is usually conical in shape, with its base in the plane of the lung's periphery and its apex pointing toward the center of the affected lobe.

Weill and Mouriquand,² from a study of 350 cases by Roentgen ray, conclude that the early shadow is usually triangular in shape, with its base always cortical and generally axillary. They have never seen a shadow that could be considered entirely central. They further state that the shadow is often present long before the signs of consolidation appear and that in some cases these signs never appear. They suggest that the nonappearance of the characteristic signs in these cases may be due to immobilization of the part or to the fact that the base of the shadow lies beneath the scapulohumeral joint.

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* Read at the joint meeting of the Philadelphia Pediatric Society, Section on Pediatrics of the New York Academy of Medicine, and the New England Pediatric Society, Philadelphia, Nov. 9, 1915.

1. Tripier: *Traité d'Anatomie Path. Gen.*, Paris, 1904, p. 213.

2. Weill and Mouriquand: *Ann. d. méd. et chir. inf.*, Paris, xvii, 275.

In this study, in order to simplify the problem, all cases complicated by the presence of fluid in the pleura have been excluded. This leaves thirty-seven cases of uncomplicated lobar pneumonia. These all showed definite shadows, which were always quite dense and uniform, and usually definitely outlined. In every case the shadow was so situated

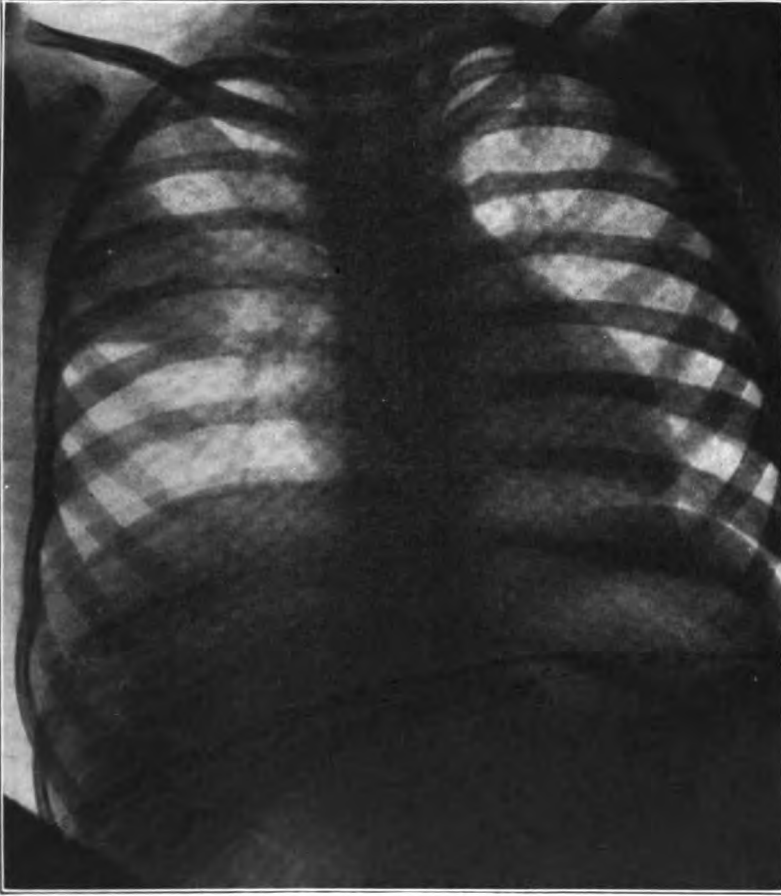


Fig. 1.—(10975) M. S., fifth day. No dulness and no bronchial voice or breathing. Some of these exposures were made in the prone position and some in the supine. This reverses the shadow in some prints.

that the consolidation must touch the pleura at some point. One patient, however, did not show a shadow five hours after the initial chill. A second negative was taken on the third day of his illness and showed a typical dense shadow. Two patients who developed lobar pneumonia while in the ward, were roentgenographed on the second day of fever and both showed definite shadows at this time.

Throughout this article the term "median" has been used to designate shadows which touch the mediastinal shadow in the roentgenograms, but do not extend to the lateral margin of the lung shadow, and the term "lateral" for those shadows that touch the remaining periphery of the lung but do not extend to the mediastinal shadow. Neither of the above terms has been used for a shadow that covers an entire lobe.

As all of the patients were young children, it was found unsatisfactory to take stereoscopic roentgenograms. Accordingly, all

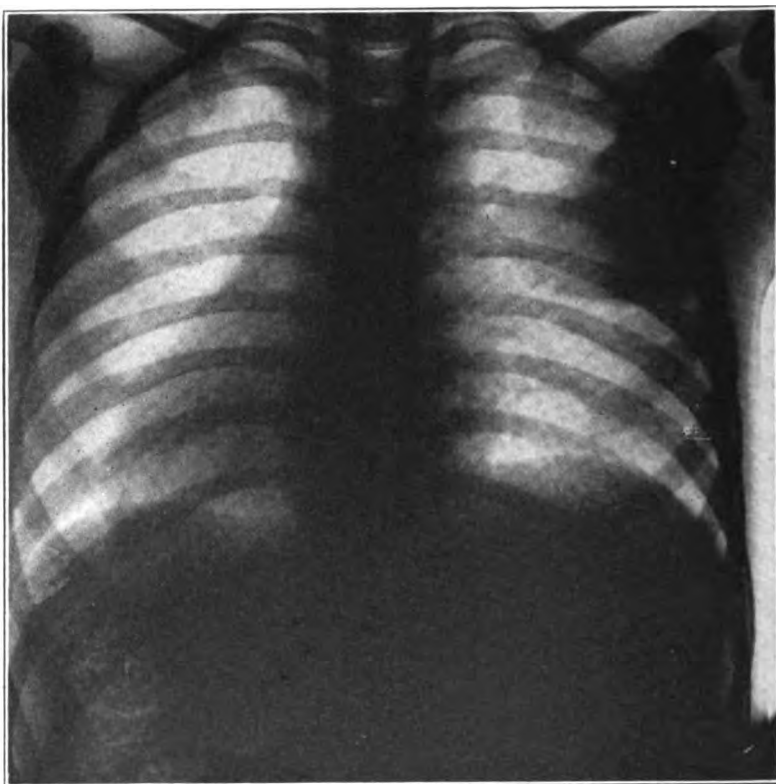


Fig. 2—(10975) M. S., sixth day. Relative dulness and diminished breathing in right axilla. No bronchial voice or breathing.

exposures were made with the child lying on either his back or his abdomen. This makes it impossible to say whether in those cases with median shadows there was normal air-containing lung between the consolidation and the chest wall and between the consolidation and the region of the root or not. In the cases with lateral shadows, the greater part of the shadow always lay close to the pleura, while the depth to which the shadow extended varied in different cases and at different

stages of the same case. Without stereoscopic negatives it is impossible to say definitely from a study of the roentgenograms that the more median portions of such shadows were not due to surface consolidation also. Physical signs, however, helped to settle this point. In the cases with lateral shadows, the early dulness was present over the base of the triangle; that is, over the lateral part of the shadow and not over the more median portion of the shadow as it should have been if this part of the consolidation were close to the chest wall.

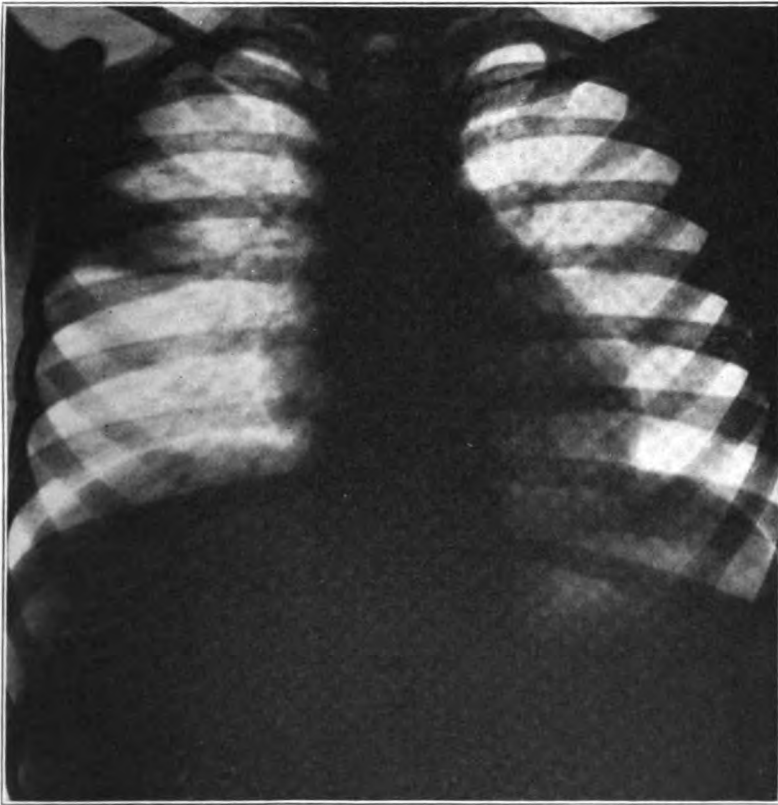


Fig. 3.—(10975) M. S., eighth day. Signs same as on sixth day, with a few moist râles.

Of these thirty-seven cases, fifteen showed in the first roentgenogram a uniformly dense shadow extending over all or almost all of at least one lobe, thus making it impossible to tell where the shadow first appeared. The first negatives of seven cases showed median shadows. In these cases also it was impossible to say how deep the consolidation extended. In both groups the shadow touched the pleura at some point. In thirteen cases the shadows were lateral, and it is the further

development of these shadows that I wish to consider. At first they were always triangular in shape, with the base on some portion of the periphery of the lung and the apex directed towards the root of the lung. The most frequent site of the base of the triangle was opposite the upper part of the axilla. From day to day they usually spread upward and downward and towards the root, gradually increasing until just before the crisis. Occasionally they spread on the surface

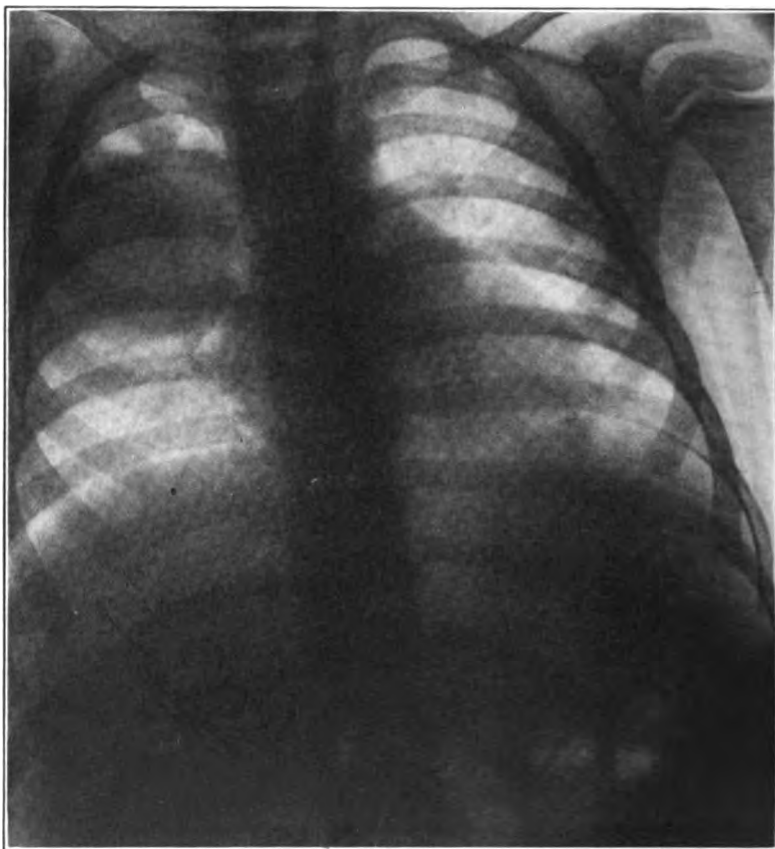


Fig. 4.—(12187) E. S., sixth day. Dulness but no bronchial breathing or voice.

of the lung but not towards the root. In the early stages there was a relatively clear area between the apex of the shadow and the root of the lung. As the shadow spread it obliterated this clear area, until in most cases there was a uniform dense shadow extending from the lateral surface of the lung to the root.

That is to say, in the beginning of the process there is a triangularly shaped shadow with its base on some portion of the lung periphery

and its apex pointing toward the hilum. This shadow is separated from the root by normal lung shadow. Gradually the triangular shadow spreads up and down and towards the root into the normal area until, as a rule, most of one lobe is involved. In trying to visualize the nature of the anatomic change in the lung, Tripier's description helps us. At first there is a small conically shaped consolidation, the base of the cone lying in the plane of the lung periphery and the apex of the cone pointing toward the hilum. This cone of consolidation gradually

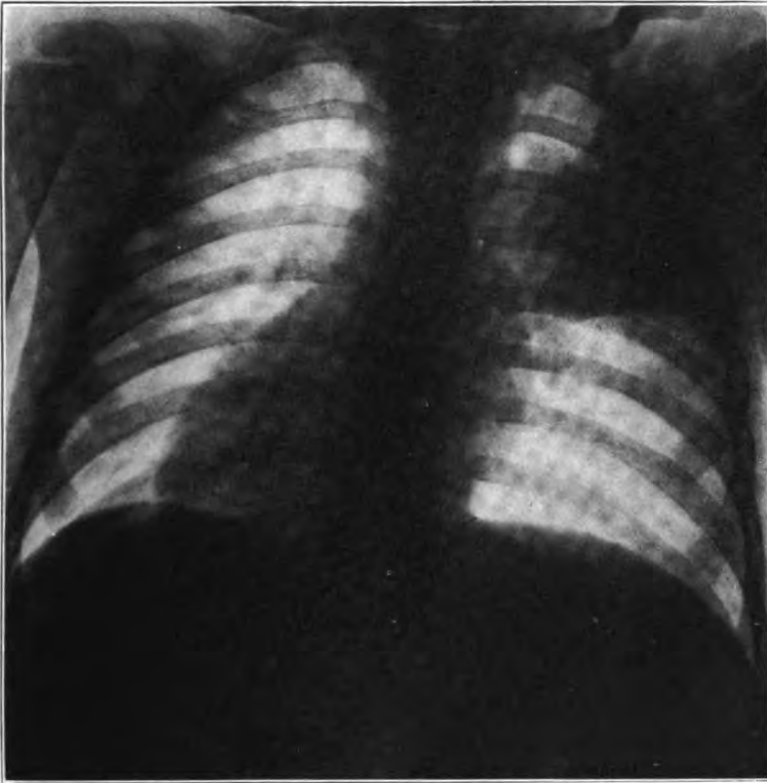


Fig. 5.—(12187) E. S., seventh day. Dulness and bronchial breathing and voice.

becomes larger and larger until finally its apex reaches the hilum and its base coincides with all, or with a large part, of the pleural surface of the lobe. The process seems, therefore, to begin in that portion of the lung which is anatomically farthest from the hilum, that is to say, that part of the lung which lies close to the pleura. To be sure the early consolidation may lie along the mediastinal pleura, or the diaphragmatic pleura or the pleura of an incisure. The fact which I desire to emphasize is that the consolidation always begins in that portion of the lung

which lies close to the pleura. Such a consolidation, when situated on the mediastinal or diaphragmatic surface of the lung may be separated from the chest wall by normal air-containing lung and in this sense may be central. On the other hand, this conception is not the same as that usually understood when so-called "central pneumonia" is spoken of, the term central pneumonia being in this sense restricted to consolidation which does not touch the pleura at any point. Weill and



Fig. 6 (12187) E. S., eighth day. Dulness and bronchial breathing and voice.

Mouriquand agree with this point of view when they say that they have never seen a shadow that could be interpreted as due to a central pneumonia.

The shadows which I have described and the anatomic changes which they indicate, suggest the explanation for the occurrence of certain physical signs with which we are familiar.

In all of the fifteen cases that gave dense shadows extending from the lateral surface of the lung to the region of the root in their first

roentgenograms, there were bronchial voice and breath sounds. Thirteen cases showed only lateral shadows at the first examination and in none of these were bronchial voice and breath sounds detected. Ten of these patients were examined again later when additional roentgenograms were made. Eight of the ten developed bronchial breath and voice sounds later. In all eight cases these signs did not appear until the shadow extended to the region of the root. The shadow in the two cases that did not develop bronchial signs did not extend to the hilum, but the shadow in these cases was always separated from the root by an area of normal lung shadow. Unfortunately no subsequent roentgenograms were made in the remaining three cases.

In all these cases bronchial voice and breath sounds were present when the shadow extended from the lateral surface of the lung to the region of the root, and they were absent when the shadow was separated from the region of the root by an area of normal lung shadow.

Nine cases are not included in the above. Seven of them showed median shadows in their first roentgenograms. Three of the seven gave bronchial signs at the time the first negatives were taken, while the remaining four all developed bronchial signs later. The other two cases had shadows on the left side, the median extent of the shadows being obscured by the cardiac shadow. In these nine cases, because of their position, it was impossible to determine whether there was continuous consolidation from the chest wall to the region of the root.

There can be little doubt that those cases with continuous shadows from the lateral surface of the lung to the region of the root, have corresponding areas of consolidation. These facts furnish an explanation for the presence of bronchial signs. Tyndal has shown that sound is conducted much better through a medium of uniform density than through one of varying density. Bronchial breath and voice sounds are normally present over the trachea and large bronchi, but they are not conducted to the rest of the chest. In the first case, the sounds traverse solid tissue of a comparatively uniform density with little loss in quality or change in intensity, while in the latter case they pass through many layers of tissue and air of altering density, the repeated changes from air to tissue being accompanied by loss of the original quality.

When the medium is uniform, therefore, there is bronchial breathing and voice. If, however, the consolidated lung extends only part way from the stethoscope to the hilum, the loss in quality is great and the breath and voice sounds are not bronchial.

Thus, in the fifteen cases with shadows from the lateral surface of the lung to the root, the situation of the shadows suggested that the consolidation was so placed as to cause bronchial breathing and voice

over the consolidated area. In the thirteen cases where the shadows were merely lateral at first, the bronchial breath and voice sounds did not appear until the shadows and the consolidation bridged the area of normal lung to the root and supplied a medium of uniform density.

The same explanation can be used to account for the presence or absence of bronchial breath and voice sounds in cases with pleural effusion. If the lung beneath the fluid is airless, due to any cause (compression, consolidation, tumor, etc.), the sound traverses a medium of comparatively uniform density and suffers little loss. In these cases the voice and breath sounds over the fluid are bronchial. If the lung beneath the fluid contains air, the loss of sound is great and bronchial voice and breath sounds are not present. Montgomery and Engelhardt³ have come to the same conclusion.

SUMMARY

Thirty-seven cases of lobar pneumonia were studied with the Roentgen rays, most of them repeatedly. All thirty-seven cases showed a definite shadow.

The shadow was always so placed that it touched the pleura at some point.

The early shadows were triangular in shape, with their bases on the pleura and their apices separated from the region of the root by normal lung.

In their later development the shadows extended in size and became uniform from the periphery to the root of the lung. When the shadow involved this entire stretch, bronchial voice and breathing were present, but not otherwise. It is believed that the inference is justified that the dimensions of the shadows correspond to the extension of consolidation.

CONCLUSIONS

The following conclusions may, therefore, be drawn:

1. The consolidation of lobar pneumonia in children begins in that portion of the lung which lies just beneath the pleura.
2. A central pneumonia in the strict sense never occurs. Silent consolidations are subpleural consolidations and are separated from the hilum by normal lung.
3. Bronchial breath and voice sounds are dependent on the presence of a medium of comparatively uniform density from the site of their origin (the trachea and large bronchi) to the point where the ear or

3. Montgomery and Engelhardt: *Arch. Int. Med.*, 1915, xv, 1040.

stethoscope is applied. These conditions are fulfilled when the consolidated area extends from just beneath the ear to the region of the hilum.

PROTOCOLS OF CASES WHOSE ROENTGENOGRAMS ARE SHOWN
IN THE ILLUSTRATIONS

No. 10975. M. S., girl, aged 4½ years. Admitted on the fourth day of illness. Crisis on the sixth day. Leukocytes fifth day, 48,000; polynuclears, 88 per cent. Fifth day, no dulness and no bronchial voice or breathing. Roentgenogram shows right lateral shadow extending a little more than half the distance to the root. Sixth day, day of crisis, relative dulness and diminished breathing in right axilla. No bronchial voice or breathing. Roentgenogram shows slightly less extensive shadow. Eighth day, two days after crisis, relative dulness and diminished breathing in right axilla with a few moist râles. No bronchial voice or breathing. Roentgenogram shows a less extensive shadow.

No. 12187. E. S., girl, aged 1 year. Admitted on fifth day of illness. Crisis on ninth day. Leukocytes fifth day, 33,600; polynuclears, 78 per cent. Sixth day, dulness but no bronchial breathing or voice over right upper. Roentgenogram shows extensive shadow over most of right upper, but separated from region of root by a comparatively clear area. Seventh day, dulness and bronchial breathing and voice over right upper lobe. Roentgenogram shows slightly more extensive shadow with clear area near root almost obliterated. Eighth day, dulness and bronchial breathing and voice over right upper lobe. Roentgenogram shows shadow slightly denser near root.

I wish to thank Mr. Ira L. Simms, radiographer, and Mr. C. J. Lander, photographer, for their painstaking care, without which this work would have been impossible.

134 East Seventy-Fourth Street.

RECURRENT HILUS INFILTRATION

AN UNUSUAL FORM OF TUBERCULOSIS IN CHILDREN *

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AND

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Our knowledge of the pathogenesis and the anatomic varieties of tuberculosis in childhood has undergone considerable change during the past decade, and at present we know that the clinical types of pulmonary tuberculosis in the first few years of life are quite distinct from those of adults. Typical apical lesions commonly found in adults are not seen till late in childhood, while affections of the bronchial lymph nodes are the rule. There are, however, forms of tuberculosis whose localization in the lungs of children is just as typical as that in adults, the area of lung involved being determined by the presence of the diseased bronchial nodes. It is our purpose in this paper to report clinically and from the roentgenographic standpoint one particular variety of juvenile tuberculosis which is of considerable importance.

Before describing the lesion in detail it may be well to review briefly the generally accepted conception of the origin and distribution of tuberculosis in the infant and child. The work of Hamburger, Ghon, Albrecht and others has proved that in the majority of instances tuberculosis enters the organism by means of the respiratory tract and first localizes in a small, often almost microscopic, lesion in the lung tissue itself. This focus, varying in size from that of a pinhead to an almond, is termed by Ghon the primary focus. This has been found in practically all the cases giving a positive von Pirquet reaction. Secondly from this lesion the bronchial nodes become involved and form in all probability the nidus in which the latent infection lies dormant. The disease may remain permanently in this condition, the nodes finally organizing or calcifying; or else they may act as a starting point for further pulmonary involvement. This secondary involvement may be the outcome of either a reinfection, in which case the apical and phthisical forms result, or else direct extension from the lymph nodes may take place.

The form of tuberculosis here to be described is one of such extension from the lymph nodes and occurs frequently enough to warrant

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* From the Pediatric Dispensary and the Roentgen-Ray Department of Mount Sinai Hospital.

its incorporation as a clinical entity in the great group of tuberculous infections of the lung. Sluka¹ has encountered it thirty-eight times in a few years, and Eisler² has also reported an identical clinical picture. For a knowledge of its morphology we are indebted entirely to the Roentgen ray, which discloses it with striking clearness.

This lesion occurs in the vast majority of cases on the right side and its point of predilection is the lung in the immediate vicinity of the fissure between the upper and middle lobes. Beginning with its base at the hilus, where a dark shadow of tuberculous nodes is visible, a fairly opaque shadow of homogeneous density extends outward into the lung for a considerable distance, gradually fading into the normal

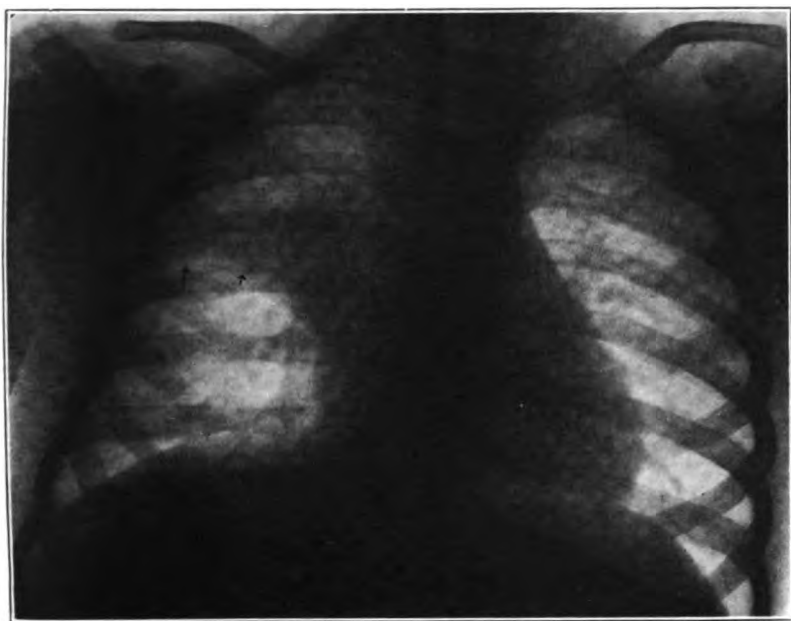


Fig. 1.—(Case 1). Radiograph of chest taken March 6, 1915. Enlarged bronchial lymph nodes surrounded by triangular infiltration at the root of the right lung. Thickened interlobar fissure indicated by arrow.

lung tissue. The resulting infiltration is triangular in shape, its apex near the axilla. Its lower margin is sharply limited by the interlobar fissure. The latter is evidently thickened and is the seat of a pleurisy,

1. Sluka, E.: Ueber Roentgenbefunde bei Tuberkulosen Kindern mit Expiratorischem Keuchen, *Wien. klin. Wchnschr.*, 1910, xxiii. Die Hilustuberkulose des Kindes im Roentgenbilde, *Wien. klin. Wchnschr.*, 1912, No. 7. Ein Weiterer Beitrag zur Hilustuberkulose des Kindes im Roentgenbilde, *Wien. klin. Wchnschr.*, 1913, No. 7.

2. Eisler, F.: Die Interlobare pleuritische Schwarte der Kindlichen Lunge im Roentgenbilde, *München. Med. Wchnschr.*, 1912, No. 35.

as it can usually be seen extending quite to the axilla beyond the limits of the infiltrated area.

Various interpretations have been applied to these shadows. They have been assumed by Eisler² to be to a great extent due to pleurisy in and about the interlobar fissure, resulting from a primary tuberculous focus in the sense of Ghon, which is so frequently found at necropsy in this situation. Sluka, on the other hand, and with greater plausibility, believes that it is a direct infection of the pulmonary tissue from the caseated lymph nodes at the hilus with a resulting tuberculous infiltration of the lung. This is rendered more likely by the following con-

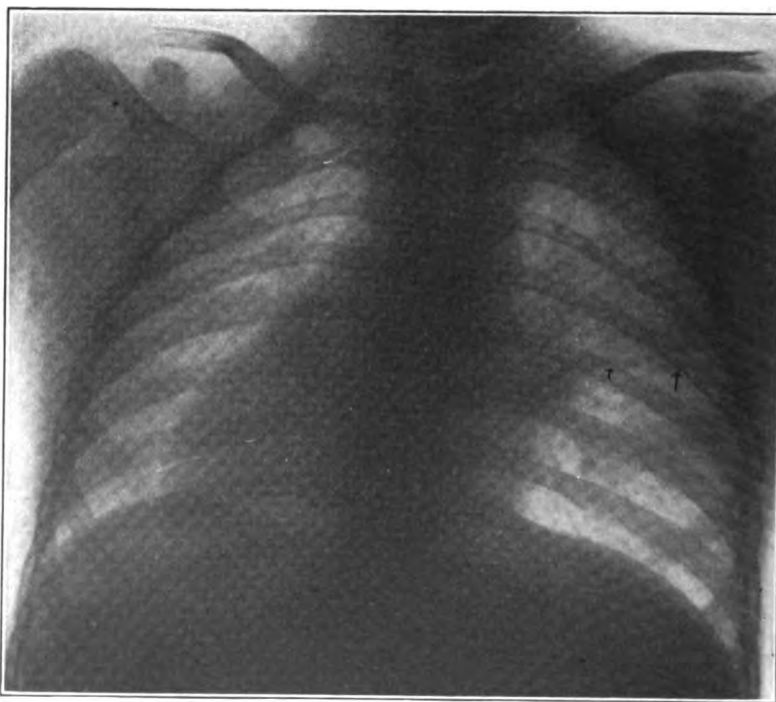


Fig. 2.—(Case 1). Radiograph taken March 25, 1915. Absence of hilus infiltration. Persistence of thickened interlobar fissure. Enlarged bronchial lymph nodes.

siderations: The primary lesion of Ghon is commonest in the first years of life. If it were responsible for this form of tuberculosis, we should encounter it frequently at an early age. It is, therefore, remarkable that Sluka in his series never found it before the age of 2 years, and we have had a similar experience in the Roentgen examination of children.

The infiltration does not remain constant in size or appearance, and this is perhaps the most remarkable fact in regard to these cases.

Most forms of tuberculosis as we encounter them in adults, are characterized by the constancy of the findings over fairly long periods of time. In these cases, the process suffers striking variations in its extent. The Roentgen examination made at intervals of a month may show at first a wide area of infiltration and at the later examination, nothing may be left but the thickened interlobar fissure. The latter usually persists for a long time as a thin, sharp line running horizontally across the upper part of the right lung from the inner end of the fourth costosternal junction to the axilla. Such a sequence of infiltrated and nor-

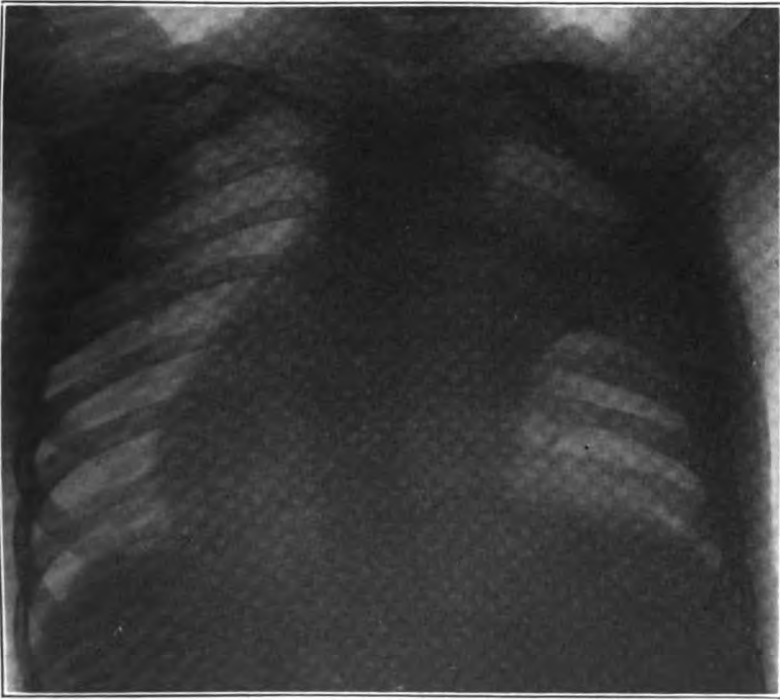


Fig. 3.—(Case 1). Radiograph taken May 8, 1915. Recurrence of hilus infiltration as in Figure 1, sharply limited below by the interlobar fissure.

mal lung may be repeated several times, and justifies the appellation of "Recurring hilus tuberculosis," and will find its correspondence in the signs and symptoms of the patient.

Tuberculosis of the bronchial lymph nodes may therefore give rise to two distinct pathologic changes in their immediate vicinity, which may occur separately or coincidently. The first is the form of infiltration described in this paper. The second is an interlobar pleuritis which frequently accompanies the infiltration and is well shown in the illustrations. This pleuritis may, moreover, occur alone and give rise to

a similar group of symptoms. Roentgen-ray examination is therefore absolutely necessary to differentiate between the two conditions.

Children in whom this typical hilus involvement has been found are usually brought to the physician on account of general debility, loss of weight, slight cough or night sweats. In childhood the condition is Physical examination of the chest is usually completely negative unless found between the ages of 2 and 8 years, not occurring in infancy. the process has involved a considerable mass of lung tissue. This is a point of the greatest importance for it emphasizes the fact that in

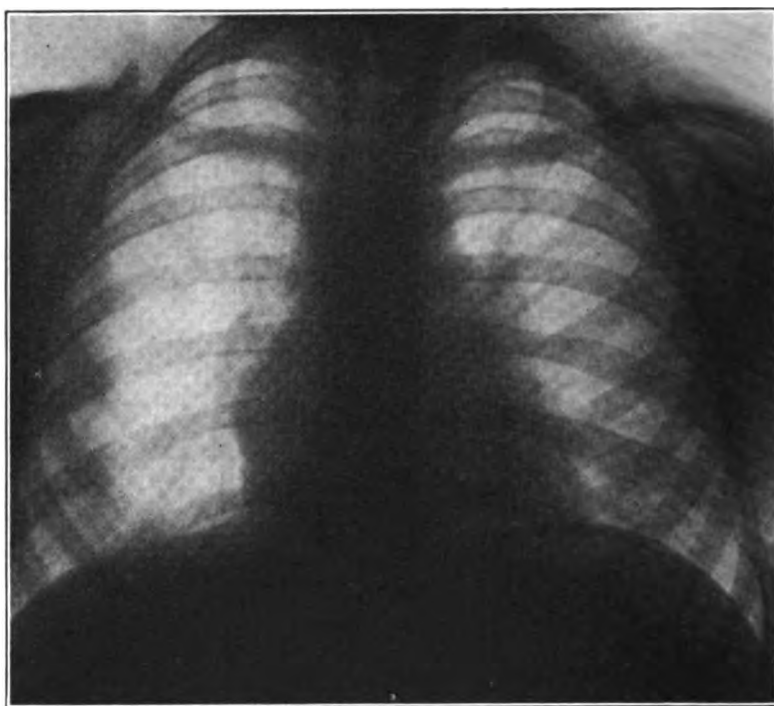


Fig. 4.—(Case 1). Radiograph taken November, 1915. Absence of all infiltration.

such debilitated children with positive von Pirquet test, Roentgen-ray examination is imperative. This is all the more necessary since it has been shown that this particular lesion is in many cases a curable one, provided appropriate treatment is followed. When the lesion is extensive, slight dulness to the right of the sternum may be present, and expiration may be prolonged, harsh and accompanied by a few fine râles. These signs though important when present, must not be relied on as we have seen involvement of considerable extent where no signs whatever were apparent.

The clinical picture of these cases is, moreover, peculiar, in that it shows considerable variation in the same case at different times. There is apparently a recurrent inflammatory process, which as it extends from the hilus into the lungs produces an exacerbation of the clinical signs and symptoms. At such times there is more rapid emaciation, more weakness, more fever and possibly more cough. It is during such exacerbations that the Roentgen ray reveals the extension into the lung fields as described above. In favorable cases, and the majority seem to be of this type, there is a distinct regression, the symptoms all becom-

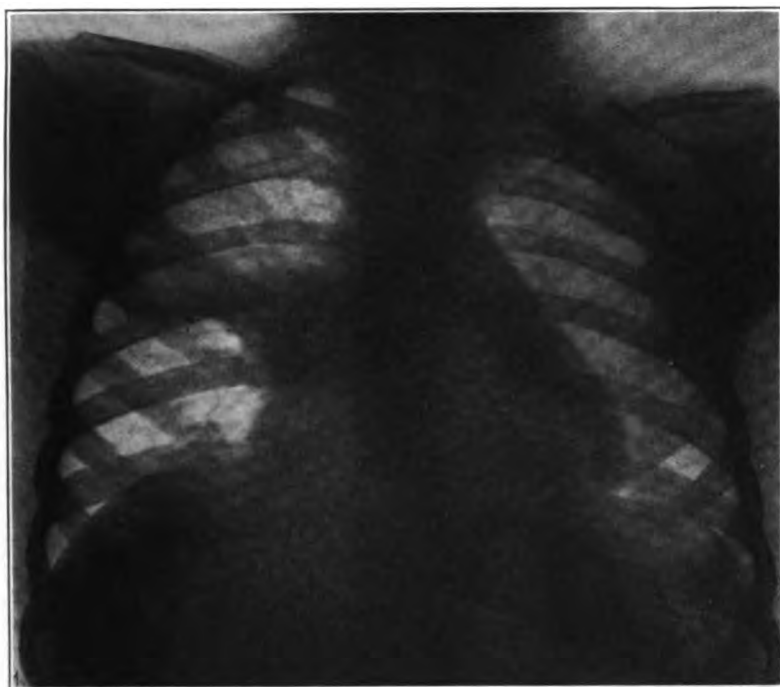


Fig. 5.—(Case 2). Radiograph taken June 3, 1915. Enlarged bronchial lymph nodes surrounding right lower bronchus. Triangular shadow of infiltration in right upper lobe bounded below by the interlobar fissure.

ing much milder, and the Roentgen-ray coincidentally showing a diminution in the amount of lung involvement. Sluka has followed many such cases through a number of similar cycles.

REPORT OF CASES

The following cases are chosen from a number observed as typical of the lesion under discussion:

CASE 1.—Sarah D., first seen November, 1914, at the age of 3 years. Family history negative; no exposure to tuberculosis. The child had always been well

till three months before coming under our observation, when she had an attack of measles, followed by "pneumonia." Since that time the child has had a cough and has not appeared to be in good health.

November 21, 1914. Child rather poorly nourished. Except for slight general glandular enlargement, physical examination negative. Pirquet strongly positive. Weight 35 pounds.

December 17, 1914. Still coughing and running very slight temperature. A few râles to be heard in the right chest posteriorly at the angle of the scapula. A roentgenogram taken at this time shows enlarged bronchial lymph nodes and a linear shadow of a thickened right interlobar fissure.

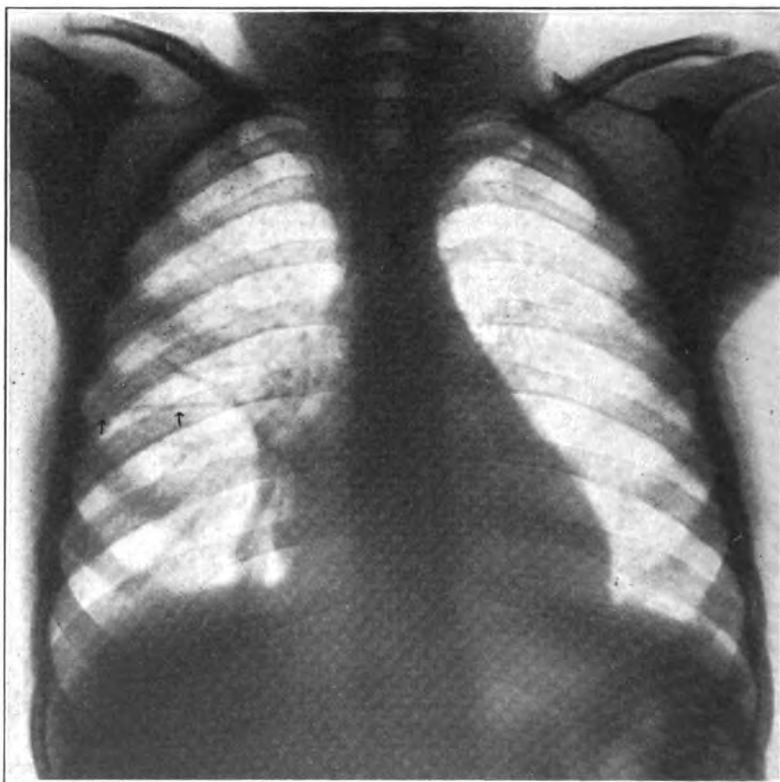


Fig. 6.—(Case 2). Radiograph taken June 29, 1915. Disappearance of the infiltration present in Figure 5. Note the persistence of the interlobar fissure which is well shown throughout its entire extent.

January 16, 1915. Cough persists.

March 6, 1915. Recently child has begun to complain of dull pain in the right side of chest. There is slight dulness and bronchovesicular breathing over the middle portion of the right chest posteriorly. The Roentgen-ray shows distinct consolidation in the region of the interlobar fissure between the right upper and middle lobes. (Fig. 1.)

March 25, 1915. Feeling much improved. Cough improved, but still present. Gained in weight. Physical signs now show only somewhat roughened breath-

ing over the middle lobe. Roentgenogram (Fig. 2) shows a resorption of the process, leaving only a thickened interlobar fissure.

May 8, 1915. After an interval of about six weeks during which the child was in apparently good health, the symptoms again recurred. Physical signs same as during last attack. Roentgenogram (Fig. 3) shows a recurrence of the infiltration, which has the same distribution as at the previous exacerbation, but is more extensive.

November, 1915. After the last attack the child was sent to the mountains where she improved rapidly. Has been well since then. No coughing. No

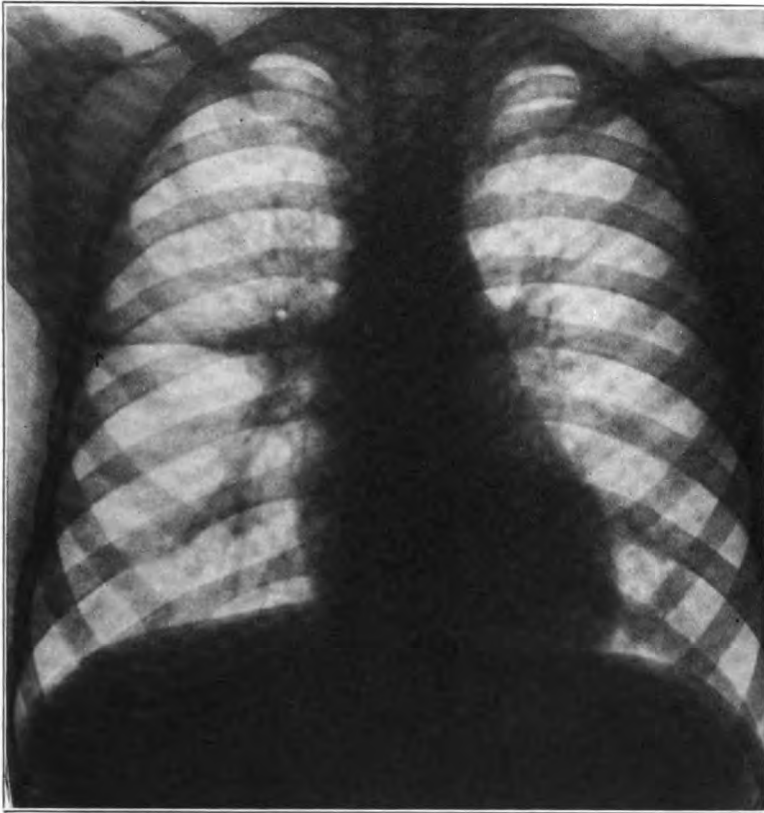


Fig. 7.—(Case 3). Interlobar pleurisy. Dense shadow along the interlobar fissure. Note the width of the shadow peripherally, as shown by the arrow.

fever. Physical condition is now excellent. Has gained rapidly in weight; weight now 46½ pounds. Color good. Nutrition excellent. Examination of lungs reveals no abnormality whatever. The Roentgen-ray examination shows enlargement of the bronchial nodes, but no infiltration of the lung. (Fig. 4.)

CASE 2.—Minnie C.² Aged 6 years. History negative except that three years prior to this report she had an acute pulmonary condition accompanied

3. From the dispensary service of Dr. M. Taschman, through whose courtesy we report this case.

by cough, fever and vomiting. Since then she has had recurrences of such attacks every few months. In the interval she is apparently well.

June 3, 1915. Fairly well nourished child, small for her age. The only physical finding worthy of note is dulness in the middle of the right chest anteriorly and posteriorly. No changes in breath sounds. Pirquet test positive. Roentgenogram (Fig. 5) shows a triangular shadow at the right hilus, with a marked thickening of the interlobar fissure.

June 29, 1915. The child is apparently well again and has neither symptoms nor physical signs. Roentgenogram (Fig. 6) shows a persistence of the interlobar fissure but no pulmonary infiltration.

Pleurisy of the interlobar fissure, which may give rise to symptoms very similar to those found in the cases of hilus infiltration, is well illustrated in Figure 7, the plate of a 6-year-old tuberculous child, who for four years has had recurring attacks of cough, fever and sweats. Here may be noted the exudate along the fissure and infiltration of the hilus. It may be evident that to differentiate this case from those of the other group without a Roentgen examination would be impossible, as in neither case are there any marked physical signs.

The exact pathogenesis of these lesions is rather obscure, for corroboration by necropsy is impossible, since the majority of the children recover, and those in whom the lesion goes on to a fatal termination present the picture of a general caseous involvement of the lung. The histories of many of the cases have shown that before the onset of the condition the child had either measles or pertussis; and the theory has been advanced that possibly there is at this time not only a lowering of the resistance to tuberculosis, but also that local conditions in the bronchial glands may be at fault. It is well known that during the course of measles the nodes become swollen and inflamed, and it is possible that this inflammation added to the tuberculosis already present causes a thinning of their capsules and final rupture either into a bronchus or directly into the surrounding pulmonary tissue.

The fact that such regressions not only in the symptoms, but also in the Roentgen-ray findings, can take place also needs explanation. It is difficult to conceive of a true tuberculous infiltration coming and going in this fashion, and the most plausible theory appears to be that the underlying pathologic process is one of an inflammatory exudate about the tuberculous hilus. Such exudative processes have been described by Fraenkel,⁴ who ascribed them to toxin action and showed that they might resolve leaving very few traces behind them.

This condition should not be confused with interlobar pleural exudates such as have been quite recently described by Weihe.⁵ These

4. Fraenkel A.: Klinische und anatomische Mittheillungen über indurative Lungenentzündung. *Deutsch. Med. Wchnschr.*, 1895, No. 10.

5. Weihe, F.: Die Interlobare Pleuritis im Kindesalter, *Ztschr. f. Kinderh.*, 1915.

may be differentiated by the fact that they often occur in infants and in nontuberculous individuals (in Weihe's cases seven out of eight). When of considerable size they also produce more distinct clinical signs and their Roentgen-ray shadow has a tendency to appear broader at the periphery than at the hilus, the opposite of the condition as seen in our cases. In doubtful cases exploratory puncture should be performed.

From the clinical aspect, nontuberculous inflammatory processes occurring in children who have pulmonary tuberculosis are also well known, and we may quote the following from Bandelier and Roepke's⁶ "*Klinik der Tuberkulose*":

Particularly worthy of note in children with bronchial gland tuberculosis is the tendency to certain affections of the bronchi and lungs, which are in no respect tuberculous in their nature. Here belong, according to Hutinel, the disposition to simple diffuse bronchitis, frequent localized bronchitis in the lower lobes, at the apices or in the neighborhood of the hilus, also certain forms of asthmatic bronchitis, and finally pulmonic congestion which may completely simulate pneumonia, but disappear very rapidly, sometimes in the course of a few hours. We are dealing in such cases with reactions on the part of the respiratory tract, or with indirect sequelae of hilus tuberculosis. Their differentiation from focal pulmonic disease is always difficult, often only possible from a consideration of their clinical course. One should therefore be careful about hurried diagnoses and unfavorably given prognoses.

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6. Bandelier and Roepke: Die Klinik der Tuberkulose, Wuerzburg, 1914.

MESENTERIUM COMMUNE WITH ABNORMAL COURSE OF JEJUNUM

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Congenital anomalies of the abdominal organs are now treated, not merely from an exclusively anatomic standpoint as curiosities, but have been given especial attention since the development of the embryology and teratology, and particularly since the advance in abdominal surgery. Displacements and malformations of the intestinal tract, in the first place, may have great diagnostic interest and may present problems complicating operative technic. Cases observed clinically or anatomically with exactitude therefore possess a practical interest beside a theoretical value, and the surgeon must ever be prepared to meet such anomalies and deal with those variations of normal abdominal topography depending on them.

As a contribution to this teratologic topic I report the observation of the following case, in which congenital anomalies were detected at the anatomic section of the pediatric course at the Rush Medical College.

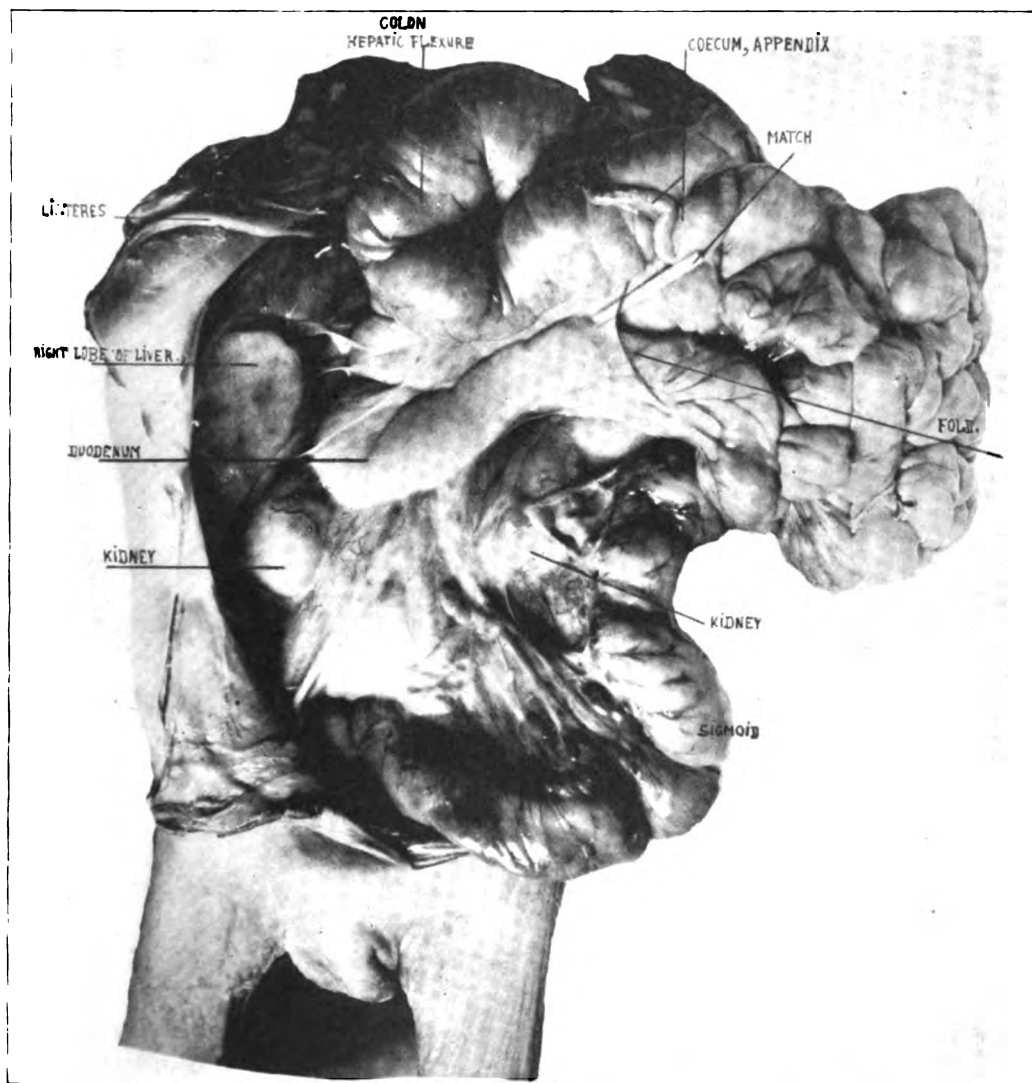
Boy, 1 year old, died from "decomposition" and pneumonia, Oct. 14, 1915, in the Cook County Hospital.

On opening the abdomen loops of small intestine present themselves, entirely covering the colon ascendens and transversum, with the exception of the hepatic flexure. On removal of the convolutions of the small intestines the cecum with the appendix appear in the region of the lower pole of the left kidney, and prove to be completely and freely mobile. This position naturally must be considered merely as accidental. The colon ascendens has its course from here upward and to the right to the hepatic region. It is completely free and mobile, without any fixation to the posterior abdominal wall, and has a long mesentery in common with the ileum and transversum, so that the intestines can be drawn far upward and placed on the chest. Two folds pass from the hepatic flexure over the duodenum to the liver and kidney, respectively.

The mesocolon transversum in the region from the duodenum to the spleen is fixed in a normal way. The flexura coli lienalis is well fixed, the spleen itself is possessed of a well-formed saccus lienalis.

The mesocolon descendens, though fused with the posterior abdominal wall, is free in the left flank, so that the colon is mobile and can be lifted up about 1 cm.; the mesentery is more than 2 cm. wide (fresh specimen) at the point where it crosses the left crista ossis ilei, and the sigmoid flexure is very long, forming secondary loops and having an unusually deep recessus sub-sigmoideus; it can be drawn 2.5 to 3 cm. beyond the right crista ossis ilei.

After lifting up the mesocolon transversum nothing of the duodenojejunal flexure is to be found at the normal site or in its proximity. Only on lifting up the mesentery of the colon ascendens and the adjoining ileum does the



Absent coalescence of colon and mesocolon ascendens with posterior wall of abdomen and with duodenum. Free colon ascendens with appendix and convolutions of ileum and jejunum turned upward. Jejunum emerging on posterior aspect of mesenterium commune from fossa, marked by match.

jejunum become visible; it emerges on the posterior surface of the ileocecal mesenteric plate from a fossa that is formed by a peritoneal fold; after lifting up also the mesentery of the small intestines, as shown in the illustration, the jejunum can be followed up to the duodenal flexure proper. The fold of the fossa starts from the mesocolon near the insertion of the appendix, crosses the jejunum and ends in the mesentery of the latter. This fossa is located below the middle of the length of the mesentery. If the cecum is brought to the normal site, the jejunum descends alongside the vertebral column, and the fossa has its place near the promontory. The part of the jejunum that is enwrapped in the plate is of course freely mobile up to the duodenum.

The radix mesenterii is very narrow and peduncle-like; taking its course with the arteria mesenterica superior, it has a very small insertion on the vertebra near the duodenum; thus the mesentery resembles a fan, the free edge of which is fringed with coils, with the narrow peduncle inserted on the vertebra.

The mesenterium ileocolicum is 5.5 cm. long measured from the ileocecal angle to the fixation of its root (preserved and much shrunk specimen). The transverse diameter of the abdomen is 11.5 cm. between the crista ossis ilei.

The arteria mesenterica superior does not, as normally, cross the horizontal, preaortic part of the duodenum, but within the root of the mesentery it ascends to the left of the duodenum toward the aorta.

The duodenum is not covered by the mesocolon, as the figure shows; its ascending portion is somewhat mobile, being incompletely fused with the peritoneum parietale of the posterior abdominal wall. The pars libera of the omentum majus, spreading over the small intestines, usually more or less apron-like, is undersized, especially in its left part. There is no ligamentum hepatorenale.

On the posterior wall of the abdomen there are nowhere scar formations, bands or adhesions visible; the peritoneum has everywhere its normal luster.

In briefly summarizing, we find the following anomalies present: mesocolon commune; duodenojejunum behind the plate of the mesocolon commune, the jejunum emerging from an abnormal fossa, and running downward along the vertebral column; abnormal course of the arteria mesenterica superior; ascending part of duodenum somewhat mobile; sigmoid flexure elongated with wide range of mobility even considering the age.

DISCUSSION

In order to understand the principal features of this anomaly, we may briefly recall to mind a few phases of the development of the mesentery and intestinal tube in the human embryo. As known, the omentum majus develops as an outgrowth of the mesogastrium, which is attached to the posterior wall of the abdominal cavity in the region of the pancreas and spleen on the one side, and to the great curvature of the stomach on the other side. By intense proliferation of this peritoneal plate a bag-like duplicature is formed, that covering apron-like the colon and small intestines reaches with its folded edge usually into the small pelvic cavity. An underdevelopment of the free part (bursa omenti) of the omentum is not rare in the adult, all degrees in size being known, from the normal type that reaches with its lower edge to the small pelvis, even to the most rudimentary development with a length of a few centimeters, or even, indeed, absence of this part. In the new-born we often find a less developed pars libera.

For the normal position and arrangement of the intestines and mesentery the process of development and rotation of the free original umbilical loop (*Nabelschleife*) as described by Toldt (1879), is important. Under normal conditions the cecum and colon which develop in the lower, recurrent segment of the *Nabelschleife* move to the right side of the abdominal cavity, the cecum descending finally to the iliac region. The mesentery of the colon ascendens (mesocolon ascendens) coalesces with the primary parietal peritoneum of the posterior abdominal wall, as likewise does the mesocolon descendens, so that only the colon transversum retains its mesentery mobile and with both its surfaces free. The formation of the normal peritoneal covering at the junction of the duodenum and jejunum is due to the rotation of the primitive umbilical loop and the resulting overlying of the root of the mesentery by the colon transversum and its mesocolon, which latter crossing the spinal column to the right side undergoes partial coalescence with the posterior wall of the abdomen.

Anomalies as described above, and similar ones, originate, because under certain conditions the normal coalescence of the mesenteries and intestinal segments with the posterior abdominal wall does not take place. This developmental disturbance affects most often the colon ascendens. In such case it is possessed of a freely mobile mesocolon, which passes without sharp demarcation into the iliac mesentery. Occasionally also the coalescence of the duodenum or of the colon and mesocolon descendens is entirely or partially absent, the segments of the intestines concerned retaining their free and mobile mesentery. The rotation of the primitive umbilical loop may also occur in the reversed direction with "*situs inversus intestini*" resulting, or it may be more or less incomplete. Cases of failure of rotation have been reported by Charles Mayo,¹ Beekman Delatour,² and Downes.³ The unusually deep recessus subsigmoideus in my case is nothing else than the unusually large residue of the originally entirely open space between the abdominal wall and the mesentery of the sigmoid flexure; the coalescence of the mesosigmoid with the parietal peritoneum being defective. It is evident that extraordinary mobility of the intestines and their mesenteries renders possible abnormal positions of these organs; by coalescence or adhesions, antenatal or postnatal, of the latter at unusual places, abnormal relations are formed, making the anomalies of position of intestines and mesentery finally permanent.

The fusion of primarily free mesenteries, as those of the colon ascendens and descendens, with the parietal peritoneum are secondary physiologic processes.

1. Mayo, Charles H.: Med. Rec., New York, March, 1912, p. 401.

2. Delatour, B. H.: Ann. Surg., 1915, lxi, 73.

3. Downes: Ann. Surg., 1915, lxi, 111.

Why these morphologic changes should be disturbed, resulting in malformations and misplacements, that is, the causal genesis, is not known with certainty. While some authors as Klaatsch and Koch⁴ consider the anomaly under discussion, as likewise an excessive growth of the colon, as atavism, others presume that abnormal length of the intestinal tube causes incomplete apposition to and fusion with the parietal peritoneum.

Mazylis⁵ describes a case of mesenterium primitivum (commune) in combination with congenital cystic degeneration of the kidneys; he also attributes the lack of the normal coalescence to the physical factor of lack of space within the abdomen due to the enlargement of the kidneys. Though in this case a causal relation between both anomalies may exist, it is interesting to take notice of the fact, emphasized in the doctrine of teratology, that in the presence of one malformation we often may expect in the same individual some other congenital anomaly; often irrelevant, insignificant and without any direct mutual connection.

The clinical significance of the mesenterium commune mobile lies in the fact that it creates a predisposition of the intestines towards twisting around the mesenterial axis and towards displacements, not possible under normal conditions. The persistence of the embryonic stage in the development of the mesentery in addition to failure of coalescence, manifests itself also in the form of its root; while normally the fixation of the radix mesenterii extends from the second lumbar vertebra obliquely towards the right iliac fossa, the radix of the mesenterium commune is usually limited only to the second lumbar vertebra and is therefore very narrow. The disproportion of the width of the loop at the insertion of the intestinal tube and at the peduncle-like radix of the mesentery undoubtedly is a mechanical factor favoring axial twist (volvulus), the more so since the entire intestinal tract inserted on the common mesentery represent so to speak one single loop, hanging on a narrow peduncle. One only needs to load the entire intestinal convolutions on the palm of the hand, holding the common peduncle between the fingers, to realize at once the great mobility, and readiness of torsion of the mesentery. This anomaly may even in the later life of the individual cause serious and even fatal conditions, especially dangerous when not early recognized, and therefore surgeons are especially impressed with the clinical significance of this condition.

The knowledge of such anomalies is important in deciding the difficult problems arising for diagnosis; cases as described above will also

4. Klaatsch and Koch: Quoted from Huebner, Virchows Arch. f. path. Anat., 1910, cci, 427.

5. Mazylis: Reviewed, Monatschr. f. Kinderh., 1913, xii, 178.

make apparent the great technical difficulties to be encountered in an operation for appendicitis, when the diseased organ is buried deeply behind the small intestines at the site of the lower pole of the left kidney. Also the congenital anomaly of the duodenojejunal loop, as represented in my type, may be of considerable interest for the surgeon, who frequently performs gastrojejunostomy. Boyd⁶ during an abdominal operation contemplating gastrojejunostomy encountered a topographic anomaly of the duodenojejunal flexure somewhat similar to the above case. The coil could not be found at the usual situation after lifting up the transverse colon and mesocolon, but emerged from under the hepatic flexure and passed vertically downwards to the right iliac fossa.

Armstrong⁷ described the observation of a duodenum with long mesentery and abnormal position; it ran to the right and turned downwards external to the hepatic flexure, ascending colon and cecum.

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6. Boyd, S.: *Brit. Med. Jour.*, 1914, ii, 507.

7. Armstrong: *Tr. Am. Surg. Soc.*, 1910, xxviii, 299.

HEMOREFRACTOMETRY IN INFECTIOUS DISEASES OF CHILDREN *

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Refractometry is yet an almost blank chapter in pediatrics. In contrast to the now numerous papers on refractometry in adults, such researches in children are rare.

On normal refractometry of blood serum in healthy children we know only the papers of Reiss¹ and Nast.² According to Reiss the refractometric index of blood serum in nurslings is lower than in adults, and this decrease agrees with about a 2 per cent. lower concentration of serum proteins. From the age of 6 to 10 months, says Reiss, the refractometric index rises and attains a definite degree, with a value varying from 1.3480 to 1.3514, as in adults. Refractometry is perhaps the best and surest means of serum protein estimation; Reiss's researches on the subject are too well known to need any detailed mention here.

In order to estimate protein concentration in blood serum, we subtract from the number read 1.33320, which is the value of n/D to distilled water, plus 0.00277, corresponding to the other substances in solution in blood serum, and then divide the remainder of the two successive subtractions by 0.00172, the refractometric variation to 1 per cent. protein solution. So if we find $n/D = 1.34872$ to be the refractometric index of a serum, we have $1.34872 - (1.33320 + 0.00277) = 0.01285$, and $0.01285 : 0.00172 = 7.41$, then the protein concentration of this serum is 7.41 per cent.

According to Nast there are in infancy five periods of protein concentration in blood serum, as follows: from 1 to 3 months; from 3 to 8 months; from 8 to 18 months; from 1½ to 5 years and from 5 to 14 years, with a progressive increase, and is the same as that in adults during the last two periods.

In order to have a paradigm for our next following observations, we have estimated blood serum-protein concentration in healthy infants with Abbe's total refractometer. Reiss's and Nast's studies were made with Pulfrich's immersion refractometer, which gives a number of five decimals, while Abbe's refractometer gives only four.

* Submitted for publication, Nov. 9, 1915.

* Read before the Brazilian Society of Pediatrics, Oct. 10, 1915.

1. Reiss: *Jahrb. f. Kinderh.*, lxx.

2. Nast: *Ztschr. f. Kinderh.*, 1914, p. 92.

My results in contrast to those of Reiss and Nast, are as shown in Table 1.

TABLE. 1.—COMPARISON OF REFRACTOMETRIC RESULTS

Age, Months	Reiss		Nast		Mello-Leitão	
	N/D	Proteins, Per Cent.	N/D	Proteins, Per Cent.	N/D	Proteins, Per Cent.
1—	1.34557 to 1.34747	5.6 6.7

1	1.34580	5.7	1.34508 to 1.34826	5.26 7.20	1.3449 to 1.3466	5.19 6.12
	1.34605 to 1.34672	5.60 6.25	1.3463 to 1.3468	6.0 6.20
2	1.34654	6.1	1.34529 to 1.34690	5.96 6.34	1.3461 to 1.3468	5.88 6.20
	1.34635 to 1.34659	6.0 6.2	1.34540 to 1.34749	5.46 6.70	1.3463 to 1.3472	6.0 6.52
3	1.34629 to 1.34740	6.0 6.6	1.3469 to 1.3472	6.36 6.52
	1.34721 to 1.34802	6.5 7.6	1.3470 to 1.3475	6.41 6.58
4	1.3470 to 1.3474	6.41 6.52
	1.34694	6.88	1.3470 to 1.3478	6.41 6.87
5	1.34766	6.0	1.34695	6.38	1.3469 to 1.3479	6.35 6.87
	1.3471 to 1.3480	6.47 7.0
6	1.34776	6.0	1.34798	6.98	1.3480 to 1.3485	7.0 7.28
	1.34884 to 1.34891	7.48 7.50	1.3482 to 1.3500	7.11 8.15
7	1.34783	6.6	1.34820	7.10
	1.34779 to 1.34823	6.88 7.12
8	1.34895 to 1.34920	7.5 7.7	1.34854 to 1.35006	7.31 8.18
	1.34894 to 1.35110	7.5 8.8
9

10	1.34895 to 1.34920	7.5 7.7	1.34779 to 1.34823	6.88 7.12	1.3480 to 1.3485	7.0 7.28
	1.34894 to 1.35110	7.5 8.8	1.34854 to 1.35006	7.31 8.18	1.3482 to 1.3500	7.11 8.15
11	1.34895 to 1.34920	7.5 7.7	1.34779 to 1.34823	6.88 7.12	1.3480 to 1.3485	7.0 7.28
	1.34894 to 1.35110	7.5 8.8	1.34854 to 1.35006	7.31 8.18	1.3482 to 1.3500	7.11 8.15
12 to 18	1.34895 to 1.34920	7.5 7.7	1.34779 to 1.34823	6.88 7.12	1.3480 to 1.3485	7.0 7.28
	1.34894 to 1.35110	7.5 8.8	1.34854 to 1.35006	7.31 8.18	1.3482 to 1.3500	7.11 8.15
18 to 60	1.34895 to 1.34920	7.5 7.7	1.34779 to 1.34823	6.88 7.12	1.3480 to 1.3485	7.0 7.28
	1.34894 to 1.35110	7.5 8.8	1.34854 to 1.35006	7.31 8.18	1.3482 to 1.3500	7.11 8.15

The results show infancy to be divided into four periods of albuminemic concentration: Under 3 months, when n/D is below 1.3470; from 3 to 8 months, with n/D varying from 1.3478; from 8 to 18 months with n/D varying from 1.3480 to 1.3485, and over 18 months, with n/D values above 1.3482. Chart 1 shows the refractometric figures of Reiss, Nast and mine.

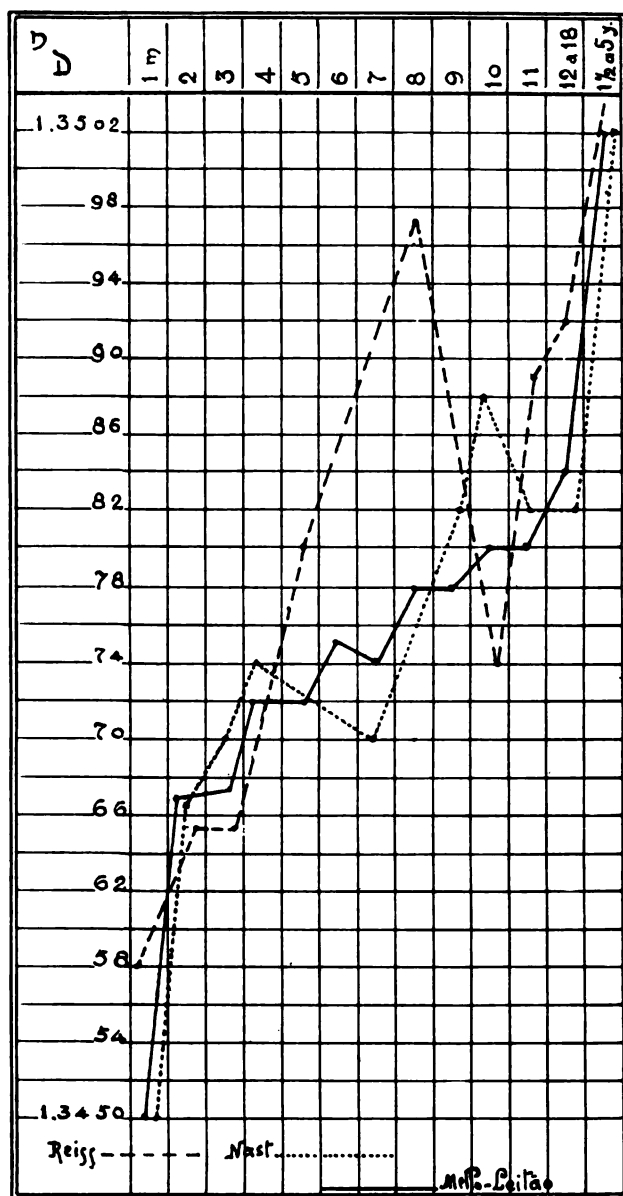


Fig. 1.—Normal refractometric index in infancy.

We have seen that as soon as the child takes table food the refractometric index rises and attains adult values, and this index varies within the same bounds after 18 months.

Refractometry of the blood in infectious diseases has been the subject of papers by Landelowski, Oppenheimer and Reiss, and Achard

and Saint-Girons. Achard, Touraine and Saint-Girons³ in their researches on rheumatism, pneumonia and typhoid fever have shown a very near relation between sickness evolution and serum protein concentration. These authors consider, in the course of an acute infectious disease, four albuminemic phases as follows:

First phase, the percentage of proteins falls more or less regularly;

Second phase, albuminemy decreases to the lowest degree;

Third phase, protein concentration rises slowly or swiftly; and in the

Fourth phase, exceeds the normal degree, descending to it again little by little.

TABLE 2.—PROTEIN CONCENTRATION IN MEASLES

Name	Age, Months	Fever Days	Eruption Day	Koplik	N/D	Proteins, Per Cent.
Olivia.....	10	4	2d	+	1.3452	5.36
Helitor.....	7	3	1st	+	1.3468	6.0
Jandyrá.....	23	4	1st	+	1.3471	6.52
Nair.....	34	3	1st	+	1.3470	6.41
Octavio.....	6	..	3d	—	1.3448	5.12
Dalla.....	18	..	4th	—	1.3470	6.41
Christovão.....	5	..	12th	—	1.3466	6.17
Luiz.....	8	..	26th	—	1.3480	7.0
Helitor.....	36	3 (39 O.)	1st	+	1.3475	6.58
		5 (37.5 O.)	3d	+	1.3463	6.0
			8th	—	1.3486	7.36
			15th	—	1.3508	8.33

In the first phase the albuminemic percentage is directly proportional to the duration and gravity of the infection; thus, in pneumonics whose disease endures from six to nine days, the least percentage of proteins was 7.224; in typhoidics, whose disease protracts itself to twenty days or more, the percentage descends to 6.771. The decrease is at first abrupt, becoming slower as it approaches the minimum, and while there is fever, the protein percentage progressively descends to the minimum and remains there.

In the second phase the refractometric index comes to minimum when the fever falls and the temperature tends to become normal; in

3. Achard, Touraine and Saint-Girons; Arch. de méd. expér. et d'anat. path., 1912, xxiv, 647.

diseases whose fever falls suddenly, the least degree of protein concentration is attained the day or the afternoon of crisis; in lysis, on the last day, when the fever decreases slowly.

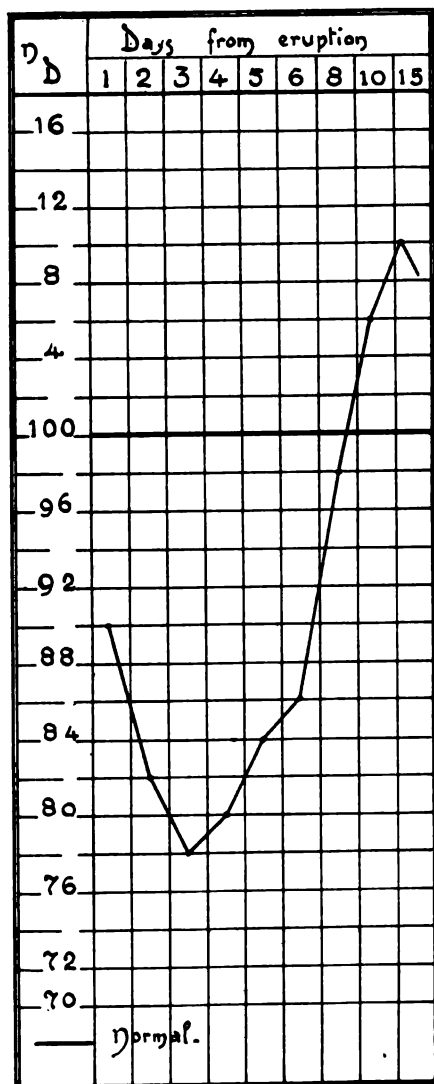


Fig. 2.—Hemorefractometry of measles as compared with the normal.

This second albuminemic phase occurs according to two clinical states. (a) It is only a slight condition, and in figures is represented by an acute angle between the descending line of the first phase and the ascending line of the third; (b) there is a more or less lasting condition,

during which the refractometric degree maintains itself constant, or with very little oscillation; in figures it is represented by a horizontal bar joining the oblique lines of the first and third phases. The first figure is observed when there is crisis, and the second when termination is by lysis.

The protein percentage rises after the day without fever, and in general this ascent is at first slow and afterward more rapid; sometimes the rise is rather sudden (only when there is crisis).

The fourth phase is not constant, but often the protein concentration goes far beyond the normal, and afterwards decreases little by little.

TABLE 3.—REFRACTOMETRIC OBSERVATIONS IN WHOOPING COUGH

Name	Age, Months	N/D	Proteins, Per Cent.	Observations
A. M.	36	1.8472	6.52	Nauseous cough since 6 days.
C. S.	4	1.8455	5.54	Nauseous cough since 3 days.
S. M.	7	1.8490	7.57	Spasmodic cough since 1 month.
S. S.	10	1.8510	8.73	Spasmodic cough since 50 days.
L. F.	11	1.8490	7.00	Spasmodic cough since 75 days.
G. N.	72	1.8489	7.51	Spasmodic cough since 6 months.
J. U.	24	1.8490	7.57	Spasmodic cough since 3 months.
U. F.	8	1.8492	7.69	Spasmodic cough since 40 days.
W. F.	10	1.8490	7.58	Spasmodic cough since 21 days.
H. A.	36	1.8500	8.15	Spasmodic cough since 7 days.
D. A.	24	1.8460	5.83	Nauseous cough 4/18/15.
		1.8468	7.46	Spasmodic cough 5/10/15.
D. C.	48	1.8487	7.40	Spasmodic cough since 10 days.
		1.8503	8.83	Spasmodic cough since 30 days.

The researches of Engel, Sandelowsky, Oppenheimer and Reiss, and Bohme all conform to those of Achard, Touraine and Saint-Girons. According to Reiss⁴ the fall of protein concentration is due to one of three causes: water retention by the organism; absolute decrease of proteins; water carriage from tissues to the blood stream. In pneumonia and scarlet fever, as shown by Oppenheimer and Reiss, refractometric figures are inversely proportional to weight figures; they have seen that in chlorid crises, weight decrease and refractometric index increase come together. Von Leyden had otherwise observed water retention in fever.

4. Reiss: *Ergebn. inn. Mediz. u. Kinderh.*, 1913, xi.

During fever there is a great protein destruction, which is indicated by an increase of nitrogen output. It is probable that the proteins of the blood stream are also raised, but we do not understand that such

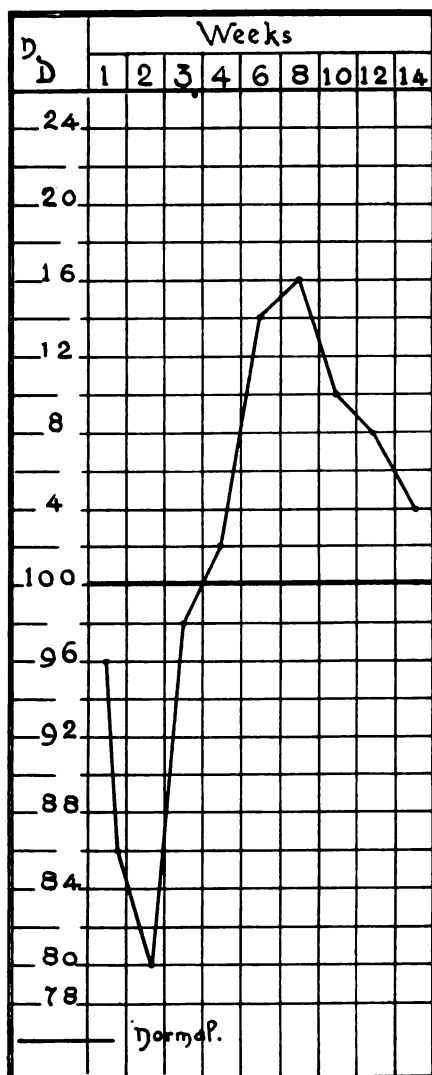


Fig. 3.—Hemorefractometry of whooping cough as compared with the normal.

destruction promotes so great a decrease of protein concentration as that observed. Reiss, however, believes this to be the cause of refractometric index decrease in cases with high fever, weight loss and no chlorid retention.

Water flow from tissues to blood in superwarming was experimentally demonstrated by Sandelowsky, but clinically we observe that fever figures in no way parallel the refractometric figures. In superwarming protein concentration rises forthwith after warming ceases, but in recovery from febrile infections the refractometric index rises little by little. Reiss believes that almost always blood dilution proceeds from water and chlorid retention.

TABLE 4.—REFRACTOMETRIC INDEX IN LATENT AND SURGICAL TUBERCULOSIS

Name	Age, Years	Weight, Gm.	Diagnosis	N/D	Proteins, Per Cent.
D. B.	½	6,500	Latent tuberculosis	1.3460	5.88
E. B.	5/12	8,000	Latent tuberculosis	1.3477	6.81
G. S.	½	6,900	Latent tuberculosis	1.3475	6.70
U. B.	¾	5,000	Adenopathy.....	1.3448	5.13
D. F.	1 1/12	7,200	Adenopathy.....	1.3458	5.71
A. A.	10/12	9,800	Adenopathy.....	1.3468	6.29
A. S.	8	24,900	Adenopathy.....	1.3482	7.11
M. J.	7	16,000	Adenopathy.....	1.3476	6.76
C. S.	7	20,000	Adenopathy.....	1.3478	6.87
V. B. C.	11	22,000	Serous pleurisy.....	1.3469	8.09
U. C.	6	13,500	Pott's disease with pulmonary tub.	1.3401	6.47
A. D.	3	12,000	Pott's disease.....	1.3510	8.73
J. J.	7	22,700	Coxalgia.....	1.3507	8.56
A. A.	9	25,000	Coxalgia.....	1.3488	7.46
W. D.	8	24,200	Serofula.....	1.3478	6.87
C. S.	2½	6,300	Pulmonary tuberc.	1.3439	4.61
H. T.	1 7/12	5,400	Pulmonary tuberc.	1.3449	5.19

It is very interesting to compare the results from observation of infectious diseases and those which have been shown by Widal, Abrami, Brissaud, Benard and Joltrain⁵ in anaphylaxis. They observed sudden fall of the refractometric index, and believe these variations to be due to physicochemic alterations of plasmatic colloids.

In order to see if in infancy refractometric figures were the same as in adults, I have examined serumprotein concentration in infants and children at the Children's Hospital Dispensary at Rio de Janeiro, where I was consulting physician.

I have divided this research into two parts: on acute, and on chronic infectious diseases. Concerning acute diseases, I have found

5. Widal, Abrami, Brissaud, Benard and Joltrain: *Compt. rend. Soc. de biol.*, 1914.

in measles a figure identical with that of Achard, Touraine and Saint-Girons, as I show in the observations of Table 2.

The refractometric index is an excellent aid in the differential diagnosis from rubeola. In this last disease protein concentration suffers no variation as I have observed in the following case:

Ismenia V., 7 months old, had a low fever for three days, with an irregular eruption. Koplik —; Theodor +; fever 37.6 C.; $n/D = 1.3472$. Proteins 6.52 per cent. After four days the value of n/D was the same.

The refractometric index in the course of measles in regard to normal is as shown in Figure 2.

As whooping cough is an apyretic, subacute infection, it was very interesting to ascertain if the Achard, Touraine and Saint-Girons curves were here the same. Researches were made in nauseous and spasmodic periods of the disease and I observed ever a low albuminemy in the first period and a remarkable increase in the last. Table 3 gives a summary of my fourteen observations on this disease.

I have registered in Chart 3 the refractometric index variations from normal in whooping cough.

Refractometry allows here the differential diagnosis from tracheobronchial adenopathy with spasmodic cough. In whooping cough the refractometric index is, during the spasmodic period, very much increased; in tracheobronchial tuberculous adenopathy, on the contrary, it is always decreased.

Concerning chronic diseases, it is very interesting to observe the low refractometric index of tuberculosis in contrast with the high degree of hereditary syphilis. Strauss and Chajes⁶ found in eight cases of tuberculosis results permitting of no conclusions.

Engel⁷ believes the refractometric index to be almost always normal, and says:

A low refraction coefficient must be considered as a poor prognostic sign, inasmuch as it indicates a high degree of disturbance of nutrition. Particularly noticeable is the successive sinking in such cases, in which a rapid progression leads to an early fatal termination.

Nast,² in Salge's clinic, found in tuberculous children the albuminemic coefficient always increased from 0.5 to 3 per cent. I have found a fairly constant decreased refractometric index, which is, in latent and surgical tuberculosis, almost normal, and becoming lower

6. Strauss and Chajes: *Ztschr. f. klin. Med.*, 1910, p. 285.

7. Einen niedrigen Refraktions-koeffizienten müssen wir dagegen als einschlechtes prognostisches Zeichen ansehen, da dieses auf eine hochgradige Störung der Ernährung hinweist. Besonders auffällig ist das successive Sinken in jenen Fällen, in welchen jene rasche Progression in kurzer Zeit zum Exitus führt." *Wien. klin. Wchnschr.*, 1910, p. 1573.

and lower, reaching the minimum in the last periods of the disease, as shown in Table 4.

Concerning syphilis, all our records show an increased albuminemy, as will be seen from Table 5.

TABLE 5.—REFRACTOMETRIC INDEX IN SYPHILIS

Name	Age, Months	Weight, Gm.	Diagnosis	N/D	Proteins, Per Cent.
M. P.	5	6,100	H. S.	1.3499	8.09
T. G.	18	7,500	H. S.	1.3484	7.23
A. A.	10	5,800	H. S.	1.3461	5.88
N. L.	6	6,200	H. S.	1.3495	7.86
L. S.	8	6,500	H. S.	1.3481	7.05
E. C.	7	7,500	Hydrocephalus	1.3505	8.44
J. S.	10	6,900	H. S.	1.3510	8.73
E. V.	5	5,100	H. S.	1.3481	7.05
J. C.	8	5,000	H. S.	1.3505	8.44
J. U.	11	6,600	H. S.	1.3485	7.28
D. L.	8	6,800	H. S.	1.3500	8.15
T. S.	3	4,400	H. S.	1.3480	7.0
D. V.	6	4,600	H. S.	1.3480	7.0
M. S.	5	6,000	H. S.	1.3482	7.11

In the observations in Table 5 we find an exception in A. A., aged 10 months, with only 5.88 per cent. as the value of the blood-serum-protein coefficient. This infant was atrophic (weighing 5,800 gm.), with alimentary decomposition and signs of tuberculous adenopathy.

CONCLUSIONS

1. The refractometric index of blood serum in nurslings is lower than that of the adult, and increases slowly from the first month till the age of 13 to 18 months, reaching then a definite value.

2. Achard, Touraine and Saint-Girons' albuminemic curve is constant in acute infectious diseases of infancy and childhood.

3. The spasmodic period of whooping cough produces high albuminemy, which permits the diagnosis from tuberculous tracheo-bronchial adenopathy.

4. The hemorefractometric coefficient in tuberculosis is generally lower than normal.

5. Syphilis increases remarkably the protein percentage in blood serum.

In conclusion we wish to express our thanks and indebtedness to Dr. Fernandes Figueira, director of the Children's Hospital.

A STUDY OF THE BLOOD IN TUBERCULOUS MENINGITIS *

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A lack of uniformity in the blood picture in tuberculous meningitis has been frequently noted in the Babies' Hospital during the last three or four years. The variations were so frequent and inexplicable that an effort was made to establish an average figure for the blood count in this condition. For this purpose 169 cases of tuberculous meningitis from the records of the hospital for the last eight years were analyzed. In the course of this work additional facts of interest were obtained, and as they help in some measure to explain the variations in the blood picture of the disease in question, they are worthy of record.

There were 252 counts made on the 169 cases. The average leukocyte count was 20,900 per c.mm. with an average polynucleosis of 72.6 per cent. Only ten, or 4 per cent., of the counts were below 10,000, and twenty, or 8 per cent., were above 30,000. The lowest total count was 5,400, and the highest 70,000—the latter occurring in an uncomplicated case. The polymorphonuclear percentage ranged from 26 to 91. The age of the children varied between 2 months and 4½ years.

It was thought that the variations in the blood picture might be explained by the presence or absence of an added infection, but an attempt to establish this relationship was not successful. For instance, there were four cases showing at some stage of the disease a blood count of 50,000 or over; but none of these cases had any clinical evidence of secondary infection. Three of these came to necropsy where the clinical findings were confirmed.

The correlation of the leukocyte count and the stage of the disease was next undertaken. The result is shown graphically in Chart 1. The broken line indicates the polymorphonuclear percentage and the solid line the total leukocyte count. The upper figures at the bottom of the chart indicate the number of counts made to determine the average polymorphonuclear percentage, and the lower figures the number of counts made to determine the average total leukocyte count. Observations on a number of cases had to be discarded because of the uncertainty of the exact date of onset of the disease. The symptoms that were of most value in fixing the onset were, in order of importance,

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(1) vomiting, (2) convulsions or twitchings, (3) drowsiness. There were a few counts made in what was judged to be the fifth or sixth week of the disease, but the number was too small to admit of any deduction.

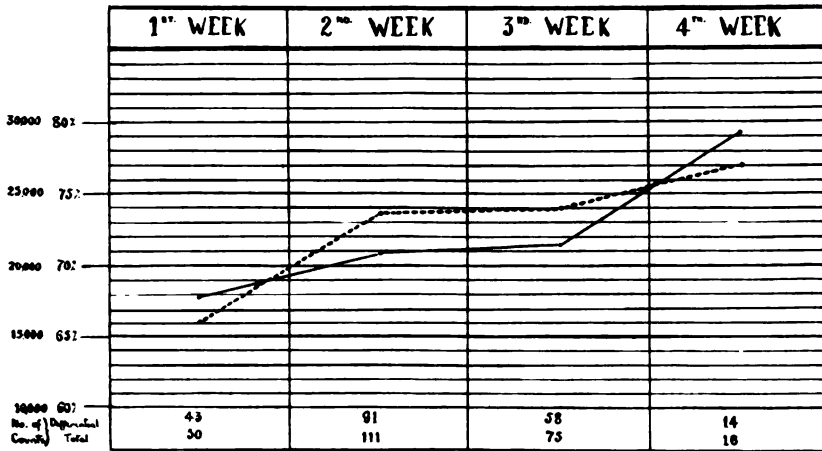


Chart 1.—Showing the gradual increase of the leukocyte count and polymorphonuclear percentage from the first week to the fourth week of the disease.

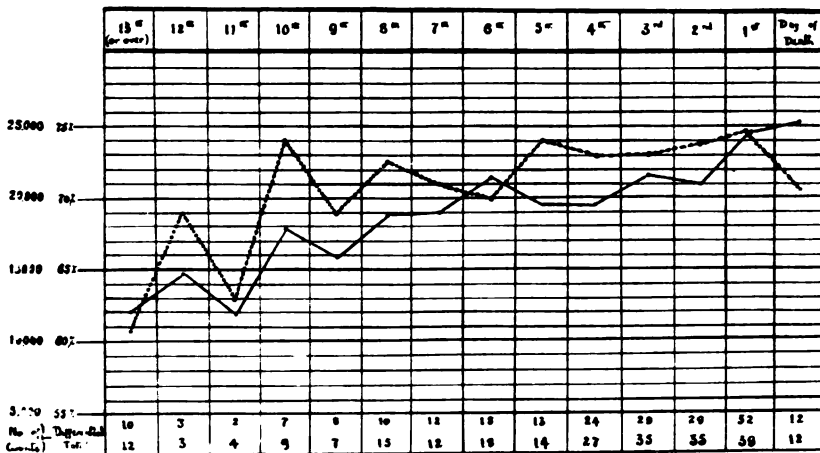


Chart 2.—The average leukocyte count and average polymorphonuclear percentage on the successive days before death, showing the gradual rise as death approaches.

Chart 2 shows the same facts from another point of view. The blood counts on the day of death, the day before death, etc., up to the thirteenth (or over) day before death were grouped together and averaged. The irregularity in the polymorphonuclear percentage curve

in the first four divisions of the chart is no doubt due to the fact that the number of counts was too small to give a very reliable average.

Chart 3 shows the blood picture of a typical case. These figures were kindly lent me by Dr. Charles Hendee Smith.

The observation that an increase in the polymorphonuclear percentage occurs in cases of tuberculosis which are progressing unfavorably is by no means a new one. Many observers, both in this country and abroad, have reached similar conclusions, but have based them on a study of cases of pulmonary tuberculosis. In such patients it is difficult to eliminate the possibility of a secondary infection in the lungs as the determining factor in the production of the increased polynucleosis. In tuberculous meningitis, however, a secondary infection is unusual, and for this reason the foregoing results are of consid-

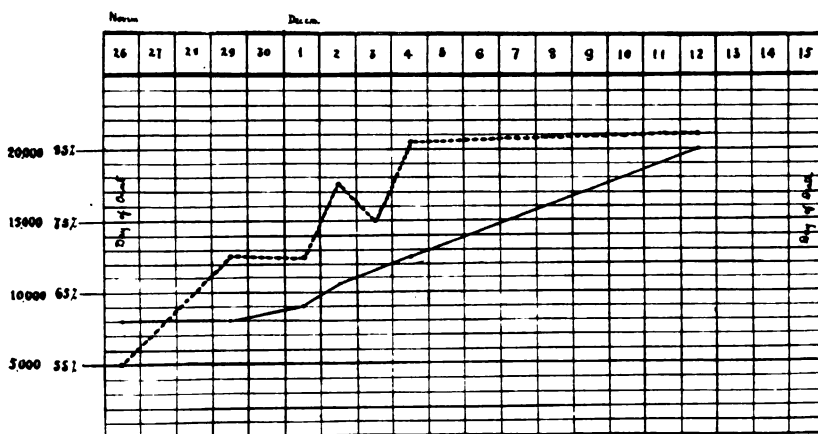


Chart 3.—The blood count in a typical case.

erable confirmatory value. These results differ from those obtained in pulmonary tuberculosis in one respect. In the latter disease, increase in the total leukocyte count has been slight, which indicates that the increase in the percentage of polymorphonuclear cells has taken place at the expense of the mononuclear cells. In tuberculous meningitis, however, as an analysis of the above figures shows, the increase in the polymorphonuclear percentage is accompanied by a parallel increase in the total leukocyte count, so that the total lymphocytes remain practically stationary. This fact makes it more difficult to offer an adequate explanation for the changes in the blood.

The character of the tuberculin skin reaction is to some extent an index of the resistance of the patient to the tuberculous infection. In several cases in this series the skin test was made every second day during the child's stay in the hospital. It was interesting to observe the gradual diminution in the intensity of the reaction as the disease

advanced. It seemed reasonable to expect a definite relationship between the blood picture and the intensity of the tuberculin skin reaction. To demonstrate this, the reactions were divided into four groups, (1) strongly positive ($++$ or $+++$), (2), positive ($+$), (3) faintly positive, (4) negative. The blood counts in these cases, made at the same time the skin test was applied, were tabulated and averaged. Chart 4 shows very strikingly the results obtained.

A satisfactory explanation of the changes in the blood picture in tuberculosis has already been advanced. Murphy and Ellis have shown the importance of the lymphocytes in the protection of the body against the tuberculous infection. These cells exert their protective action by virtue of a ferment of lipolytic power, capable of splitting wax and fat

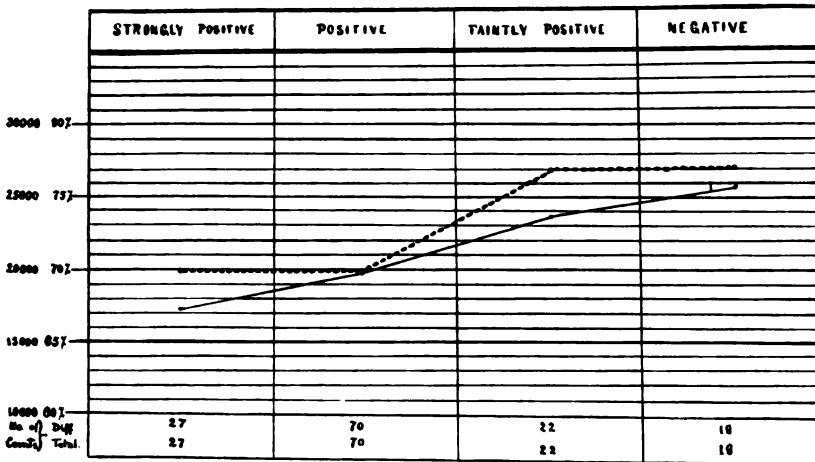


Chart 4.—Showing the relationship between the intensity of the tuberculin skin reaction and the height of the leukocytic count and polymorphonuclear percentage.

into glycerin and fatty acids. It is known that approximately 30 per cent. by weight of the tubercle bacillus is composed of waxy substances, which are broken down by means of this so-called "lympho-lipase," thus rendering the organism susceptible to digestion by the phagocytes. The chronicity of tuberculosis has been thought to be due to the difficulty the defensive mechanism of the body must have to destroy this waxy substance. An increase, then, in the lymphocytes of the blood is usually coincident with improvement in the patient's condition; and conversely, as the patient grows worse, the proportion of polymorphonuclear cells increases at the expense of the lymphocytes.

The figures obtained in this study are of interest from a scientific point of view, but are of less practical value. In the differential diagnosis of obscure cases with meningeal signs, however, it may be of

no little help to know that a blood count of 20,000 to 30,000 with a high polymorphonuclear percentage does not by any means exclude tuberculous meningitis.

CONCLUSIONS

1. The leukocyte count in tuberculous meningitis is higher than has been heretofore described. The average in this series was 20,900 per c.mm. with 72.6 per cent. polymorphonuclears.

2. The total leukocyte count and the proportion of polymorphonuclear cells vary with the stage of the disease; e.g., both counts increase as the disease advances. There is a relative but not absolute diminution in the mononuclear elements of the blood.

3. There is a definite relationship between the intensity of the tuberculin skin reaction, on the one hand, and the total leukocyte count and polymorphonuclear percentage on the other. Diminution in the former is usually accompanied by an increase in the latter, both being evidences of a failing resistance by the body to the tuberculous infection.

I am indebted to Dr. L. E. Holt for permission to publish this study, and to Dr. Charles Hendee Smith for his kindness in lending me the record of the blood examinations shown in Chart 3.

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A RAPID METHOD FOR THE DETERMINATION OF FAT IN FECES *

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An important aid in the study of fat digestive disorders of infants and young children is a quantitative estimation of the fat of the stools. Also it is frequently desirable to be able to follow the fat output from day to day as a guide to rational feeding. McClanahan and Moore¹ say:

We occasionally find cases which seem unable to digest the smallest quantities of fat. They may however have their fat tolerance gradually increased by carefully increasing the fat content of their food as they seem able to digest it. In these cases an increase in the total fat in the stools, especially if persistent and rising, is an indication for the lowering of the fat percentage of the food.

A prime necessity in the study and treatment of such cases is a rapid and easy method for the determination of the feces fat so that necessary changes in the diet may be made promptly.

The methods now in use are unsatisfactory from a clinical standpoint because of the length of time required to make a determination. Standard methods such as the Folin-Wentworth² and the Kumagawa and Suto³ require from twenty-four to thirty hours for a determination and it would be very hard to regulate the daily feedings of infants and young children if we depended on them. A method was sought which could be carried out in a reasonably short time without a notable sacrifice of accuracy.

By means of the nephelometric principle, which has been used by Bloor⁴ for the determination of the fat in blood and milk, it has been found possible to make an accurate determination of the fat in the stools in about one hour. The method consists essentially in extracting directly with acidified alcohol and ether, filtering the extract, then precipitating the fat in a watery solution and comparing the cloudy suspension so obtained with that of a similarly prepared standard solution.

* Submitted for publication Dec. 28, 1915.

* From the Laboratories of Biological Chemistry of the Harvard Medical School.

1. McClanahan and Moore: *Am. Jour. Med. Sc.*, 1915, cxlix, 815.

2. Folin and Wentworth: *Jour. Biol. Chem.*, 1910, vii, 421.

3. Kumagawa and Suto: *Biochem. Ztschr.*, 1908, viii, 212.

4. Bloor: *Jour. Biol. Chem.*, 1914, xvii, 377; *Jour. Am. Chem. Soc.*, 1914, xxxvi, 1300.

Procedure.—The whole stool is weighed to centigrams on a previously weighed porcelain plate and then thoroughly mixed with a spatula. A dry and clean 100 c.c. graduated Erlenmeyer flask, together with a 7 cm. filter paper is weighed to milligrams. About 0.5 gm. of the mixed stool is spread out in a thin and even layer on the filter paper, then paper and flask weighed again. The difference between this weight and the original weight of flask and filter paper is the amount of stool taken.

TABLE 1.—DETERMINATION OF FAT CONTENT OF DRIED STOOLS BY FOLIN-WENTWORTH AND NEPHELOMETRIC METHODS

Dried Stool	Folin-Wentworth, Mg.	Nephelometric, Mg.	Per Cent. Difference
A	32.8	33.6	+2.3
B	54.6	55.7	+1.9
C	57.6	58.7	+1.8
D	55.4	57.5	+3.6
E	47.7	49.8	+3.2

To the flask are added 60 c.c. to 70 c.c. of a mixture of 3 parts redistilled alcohol and 1 part redistilled ether, and 5 drops of concentrated hydrochloric acid. The filter paper should be entirely immersed in the liquid. The flask is connected with a return condenser and boiled for forty-five minutes then cooled under the tap with shaking, and made up to volume with alcohol-ether, mixed and filtered. The filtrate is usually water clear, but may have a slight tinge of green or brown.

TABLE 2.—COMPARATIVE FAT DETERMINATIONS ON MOIST STOOLS, USING THE KUMAGAWA-SUTO AND NEPHELOMETRIC METHODS

Moist Stool	Kumagawa-Suto, Per Cent. Fat	Nephelometric, Per Cent. Fat	Per Cent. Difference
A	10.7	10.6	-1.0
B	19.1	18.7	-2.0
C	12.4	12.8	+3.2
D	9.1	9.3	+2.2
E	8.3	8.9	+7.2
F	13.1	13.6	+4.0
G	15.3	15.8	+3.2
H	8.7	8.4	-3.4

Determination.—Five c.c. of the extract are measured from a pipet, with stirring, into a small beaker containing 50 c.c. of distilled water. In the same way 5 c.c. of a standard fat solution (see below) are added from a pipet, with stirring, to another small beaker containing 50 c.c. distilled water. To the standard and to the test solutions are added simultaneously 10 c.c. portions of dilute (1:4) hydrochloric acid with stirring. The solutions are allowed to stand for five minutes, after which they are transferred to the comparison tubes of the nephelometer.

The two tubes are filled to the same height with the solutions and are placed in the nephelometer with the standard tube always on the same side. (If bubbles appear on the walls of the tube it is important that they should be removed by inverting the tube two or three times. At the end of the readings again examine the tubes for bubbles and if they are present the tubes should again be inverted and another reading made.) The moveable jacket of the standard is usually set at 50 mm. (on the original Richards nephelometer)⁵ or at 30 mm. in a modified Duboscq colorimeter as described by Bloor.⁶ The comparison is made by adjusting the jacket of the test solution until the illumination of the solutions are equal. At least five readings are taken, alternately from below and above and the average taken as the correct reading. The readings are inversely proportional to the values, and calculations are made as in the colorimetric methods.

Standard Solution.—The standard solution used is an alcohol ether solution of equal parts of pure stearic and oleic acids, of which 5 c.c. contain about 2 mg. of fat.⁷ After trying different proportions of both we found that equal amounts gave readings closest to the results obtained by the Folin-Wentworth and the Kumagawa and Suto methods.

The nephelometric method as above will give consistent results to within 5 per cent. of the results obtained by the older methods, and is therefore adequate for all clinical purposes.

Results.—Determinations of the fat content of dried stools by the Folin-Wentworth and the nephelometric methods gave results as shown in Table 1.

Comparative determinations on moist stool using the Kumagawa-Suto and nephelometric methods resulted as shown in Table 2.

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5. Richards, T. W., and Wells, R. C.: Am. Chem. Jour., 1904, xxxi, 235.

6. Bloor: Jour. Biol. Chem., 1915, xxii, 145.

7. The standard is most conveniently made by making separate solutions of stearic and oleic acids, each containing about 0.2 gm. in 500 c.c., then mixing smaller volumes as needed. In making the solutions the fatty acid is first dissolved in the ether, then the alcohol is added.

SIALOLITHIASIS AND SIALODOCHITIS IN CHILDHOOD *

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During the time that observations were made on a recently reported variety of sublingual gland inflammation¹ notes were kept of other affections of the salivary glands seen in children. Three cases of salivary calculus and two of chronic sialodochitis were encountered.²

In his classical work on salivary calculus, published in 1855, Thomas de Closmadeuc stated that sialolithiasis did not exist in children; its occurrence in an individual of 20 years was the youngest case recorded at that time. Since then, however, seven cases of salivary calculus in children have been reported.³ In adding those I have observed, I wish to show that sialolithiasis is not an exceedingly rare condition in children, and to depict its symptomatology in early life.

Chronic inflammation and stenosis of the salivary duct, in the form observed by me in two cases, does not appear to have been described. The affection is of some importance; in both cases the diagnosis of parotid neoplasm had been made and excision proposed. Sialodochitis bears no demonstrable relationship to salivary calculus; it is convenient, however, to discuss both affections in one paper.

For purposes of comparison, the manifestations of sialolithiasis in adults will be considered very briefly. Its frequency in adult life is suggested by some 400 cases that have been described, groups of eight or more often being reported by individual observers. Calculi are encountered most frequently in the excretory ducts; in Wharton's duct in the great majority of instances. The submaxillary gland, likewise, is the most common seat of the gland stones. A distinction between duct and gland concretions is made because it is as yet impossible to determine if duct stones are extruded gland stones, or whether the conditions are separate ones. With the calculus in either situation, inflammatory and sclerotic changes in the gland ensue.

Most observers now agree that sialolithiasis results primarily from bacterial invasion; some, however, presume that swelling of the duct, with retention and inspissation of saliva, is the primary cause, and the

* Submitted for publication Jan. 6, 1916.

1. Neuhof, H.: *AM. JOUR. DIS. CHILD.*, August, 1915, p. 94.

2. With one exception, all were seen and treated in the morning surgical clinic of Mount Sinai Hospital.

3. The reports of only three were found in a careful search of the literature. The remaining four are quoted by various authors, either without reference to their source or with references that were inaccessible or incorrect.

bacterial element secondary. In fact, the etiologic factors are ill understood at present. For example, there is no adequate explanation for the far greater incidence of sialolithiasis in the male sex, or of the preponderance of calculi in the submaxillary duct-gland system, of recurrences after removal, etc.

The symptoms of duct stones are usually more severe and well defined than those of gland stones; calculi in Wharton's duct generally result in the most pronounced manifestations. Wherever the stone is situated there are usually two periods in the symptomatology. The first is characterized by intermittent attacks of pain in the affected side of the mouth, sometimes severe enough to be dignified by the term "salivary colic." The coincident appearance of a sensitive salivary swelling is very characteristic; the mass, tense and firm, is generally in the immediate region of the calculus. Suppuration marks the second stage. Mucopurulent discharge, of varying amounts, escapes from the orifice of the duct, the latter then becoming reddened and swollen. Abscesses about the gland or duct may develop, to burrow externally or ultimately to rupture into the mouth.

A calculus situated near the orifice of a duct is readily palpable through the mucous membrane of the mouth in most instances; in the depths of the duct it is frequently but by no means invariably felt by probing the canal. The diagnosis of a gland stone, on the other hand, is chiefly based on the indirect evidence of the history and the clinical findings; Roentgen-ray examination has revealed calculi in the gland in a few instances.

Many less important symptoms and physical signs have been omitted; enough has been categorically stated to indicate that the diagnosis of salivary calculus would not be difficult if the cardinal manifestations were present regularly. On the contrary, however, the symptoms are often bizarre; acute attacks of sialolithiasis have been mistaken for alveolar periostitis, cervical adenitis, angina Ludovici, etc., and the condition, in a chronic form, has been confused with tuberculosis, gumma, and malignant disease of the salivary gland.

SIALOLITHIASIS IN CHILDREN

In the reported cases, and in two of the three I have observed, the symptoms were neither as severe as those generally seen in adults nor of as long duration before the patients came under observation. Of my three cases, two were instances of solitary calculus in Wharton's duct, the third had multiple calculi in Stenson's duct. The latter, of unusual interest, will be described first.

CASE 1.—A girl, 6½ years old, came under observation in the Mount Sinai Hospital Surgical Clinic in July, 1915 (transferred to me through the courtesy of Dr. S. Cohn). She had had measles and summer diarrhea in infancy.

When she was 2½ years old both ear drums were punctured for an acute inflammation, following grip (?). A swelling of the right side of the face developed soon after; this was termed mumps. The tumefaction, always sensitive and occasionally very painful, has never disappeared since that time. It has been of fairly constant size in summer, decidedly larger and with greater fluctuations in its proportions in the winter. Three or four times in the latter season very acute swelling, with fever, would develop, persist for two or three days, and then slowly recede.

Nine months before the patient was first seen, discharge of pus from the mouth was noted. It has continued ever since. Although usually inconsiderable, thick, and ropy, on a few occasions the discharge has been very profuse and thin. The swelling in the right cheek has been less marked and less painful since the onset of the discharge.

Examination.—The child is poorly nourished. General examination is negative. Teeth and buccal mucous membrane are normal. There is a very pronounced tumefaction of the right side of the face, outlining the enlarged parotid gland. On palpation, the gland is very firm and moderately tender; there are a few softer areas in the indurated mass. The orifice of Stenson's duct is very small and reddened, contrasting with the larger, normal orifice on the left side. By pressure on the parotid mass a little saliva mixed with considerable pus is expressed from the duct. The finest lacrimal probe could not be passed into the duct. Roentgen-ray examination was negative. In order to clear up the diagnosis it was determined to split the orifice of the duct and explore its contents.

Operation.—Under general anesthesia, the mouth of the duct was widely incised, thick mucopurulent fluid escaping. A good sized probe could then be passed into the duct. At a depth of four cm. a calculus was encountered. After some manipulations the probe could be carried past the calculus to the junction of the duct with the gland. Here a second calculus was felt. Ineffectual attempts were made to extract the stones from the duct.

Course.—The parotid swelling began to diminish soon after this operation and the patient felt better. In two weeks the tumefaction had almost disappeared. The discharge of pus steadily diminished, the proportion of saliva increasing with the reduction of the swelling. The calculi, now close together, could easily be felt through the cheek and the mouth, as well as by probing the duct.

One month later the parotid swelling was practically gone, the discharge of pus had ceased, and the child was quite well except for the presence of the calculi in the duct. There was no tendency toward closure of the slit orifice. Another ineffectual effort was made to extract the stones from the duct. Evidently they lay beyond a stricture of the canal, and therefore could not be grasped and removed. An open operation for their removal was refused. When recently seen (October, 1915) the patient was still quite well. The swelling of the parotid was gone. The calculi were easily felt through the cheek.

CASE 2.—A boy, 5 years old, came under observation in the surgical clinic of Mt. Sinai Hospital in August, 1911, with a two months' complaint of pain under the tongue and along the floor of the mouth. Pain had been continuous, not severe, and not progressive. Other symptoms had not been noted. There were no previous illnesses other than measles, and nothing in the history of the case to throw any light on the cause of the present affection.

Examination.—The general physical examination was negative. The right submaxillary gland was slightly enlarged and sensitive. To the right of the frenum linguae the mucous membrane and submucous tissues of the floor of the mouth were somewhat edematous. In this area a small, firm, rounded mass (the calculus) was indefinitely felt. The orifice of Wharton's duct appeared unchanged, but a fine probe could not be introduced. Saliva could not be expressed from the duct.

Treatment and Course.—Under local anesthesia a small incision was made through the duct over the calculus; the latter was then readily extracted. Escape of thick saliva ensued. The stone was somewhat larger than a green pea, egg shaped (the small end pointing to the orifice of the duct), and of slightly irregular surface. On chemical examination (chemical laboratory, Dr. Bookman) it was found to consist entirely of calcium phosphate.

The postoperative course was uneventful. The discharge of saliva continued through the new opening of Wharton's duct. The swelling of the submaxillary gland disappeared. The remainder of the duct was probed on several occasions and found free. About two months after operation the patient disappeared from observation.

CASE 3.—A boy, 8 years old, came to the morning surgical clinic of Mt. Sinai Hospital in May, 1912, complaining of a sense of discomfort in the floor of the mouth, of one week's duration. There was no similar previous complaint. Scarlet and diphtheria when 6½ years old. There was no history of any mouth infection or injury.

Examination.—The general examination of the robust patient was negative. On the right side of the floor of the mouth, close to the orifice of Wharton's duct, a calculus could be easily felt. The overlying mucous membrane was unchanged. Saliva was not seen escaping from the unaltered orifice of Wharton's duct. The submaxillary gland was not palpable.

Treatment.—Under local anesthesia an incision was made over the calculus and was extended through the mouth of the duct. The calculus was extruded from the incision by the dammed-up saliva, which then escaped in considerable quantities. The dilated duct was probed to the gland and was found free. The calculus was slightly smaller than a lima bean, of spheroidal shape, very light and fragile, and of a spongy appearance; unfortunately it was misplaced and was not examined. The patient did not return for further treatment.

The cases of salivary calculus in childhood, whose reports in the literature are accessible, are as follows:

CASE 4.⁴—The patient, the youngest on record, was a male infant, 3 weeks old. The mother took the child to the physicians because it nursed with great difficulty. The tongue was found markedly displaced by a large, soft, sublingual swelling, presenting a firmer area in the center. A diagnosis of ranula was made. On pressing the mass, however, the tip of a calculus was seen protruding from the orifice of the duct. After several attempts the calculus was finally removed without an incision. The child remained well. The calculus was the size and shape of a grain of wheat, with one sharply pointed extremity, of yellowish color, and granulated surface. It was composed of phosphate of lime and mucus. The authors believed that it developed in fetal life.

CASE 5.⁵—Girl, 12 years old. There was a three months' history of intermittent swelling in the sublingual region. Each recession of the swelling was accompanied by a profuse discharge of saliva and a very small amount of pus. The patient complained of some interference with talking and swallowing. On examination, a calculus was found engaged in Wharton's duct. It could be rolled under the finger. About the calculus there was a soft swelling, the size of a "nut." The duct over the swelling was incised and the calculus removed. Its extraction was followed by the escape of considerable saliva, and the disappearance of the mass. Cultures from the center of the mass were sterile.

CASE 6.⁶—A boy, 13 years old. For three years there had been pain in the right side of the mouth during mastication, pain in the right cheek, and inter-

4. Burdel and Cloquet: *Comp. rend. Acad. de sc.*, No. 50, p. 893.

5. Péraire and Gaudier: *Bull. Soc. anat. de Paris*, 1898.

6. Solé: *Presse méd. Belge*, 1897, xlix, 113.

mittent swelling of the cheek in cold and damp weather. These symptoms were gradually progressive. On examination, the right cheek was found slightly swollen, the venules of the overlying skin slightly dilated. Palpation revealed a series of nodules in the course of Stenson's duct, more readily felt when the masseters were contracted. By probing, the duct was found abnormally arched. Six calculi were extracted, through an external incision of the duct. They varied in weight from 0.006 to 0.170 gm. The incision in the duct was sutured with catgut; the postoperative course was smooth and there was no leakage of saliva from the wound.

The remaining cases, whose reports are not accessible are: Two cases presumably reported by Schenk, one in a child 7 years old, the other in a child of 12. Wright (in a monograph on the Physiology and Pathology of the Saliva, 1892) is said to have described a salivary calculus in a child 9 years old. Reboul's⁷ case occurred in a child 9 (or 15) years old. Beyond the bare statement of the existence of salivary stone in these children the authors referring to them go no further; there are no descriptions of clinical findings or of the results of treatment.

SIALODOCHITIS IN CHILDREN

Two varieties of chronic sialodochitis have been described. They are affections of adult life; in a very few instances, however, their onset in childhood has been observed. Although they bear no relation to the type of sialodochitis I wish to describe, a short presentation of the clinical pictures may be permitted.

One variety—the sialodochitis fibrinosa of Kussmaul—is characterized by sudden and recurrent attacks of duct obstruction caused by fibrin plugs. This very rare affection is exceedingly chronic, affects Stenson's ducts in most instances, and is generally bilateral. The earliest manifestations of some of these cases date from childhood. The second type is, practically, identical in the recurrence of attacks, in its chronicity, and the almost exclusive, generally bilateral involvement of Stenson's ducts; it is chiefly differentiated by the absence of duct plugs. One case has been observed in childhood.⁸ A boy 13 years old suffered from intermittent attacks of pain and parotid swelling for about one year. The duct was dilated, considerable pus escaped from its mouth and the entire course of the duct could be readily probed.

These peculiar, very obscure (and probably constitutional) affections are the only forms of chronic sialodochitis that appear to have been recorded, either in adult life or in childhood. The type I wish to describe is characterized by a cicatricial stenosis of one Stenson's duct (the opposite one being normal), the result of an inflammation of unknown origin, by a firm, nodular enlargement of the corresponding

7. Said to have been reported in the *Echo méd des Cévennes*, 1902.

8. Noeggerrath: *Charité Annalen*, 1909, p. 176.

parotid gland, by a tendency to recurrence after slitting the mouth of the duct, but ultimate cure after the stenosis has been permanently overcome.

CASE 1.—A boy 4 years old came under observation in the morning surgical clinic of Mount Sinai Hospital in September, 1913, through the courtesy of Dr. Stephen Greenfield. There was an enlargement in the right parotid region, of five months' duration. The mass had slowly increased in size, pain in and about it had been dull and constant, some loss in weight had been noted. There were no previous illnesses other than measles at the age of 2 years, and pertussis soon after. A diagnosis of sarcoma of the parotid gland had been made and excision advised.

Physical Examination.—A poorly nourished pale child. The general examination is negative. The buccal mucous membrane is normal. The left parotid gland and duct reveal no abnormalities. The right parotid gland is enlarged to about three times the normal size; is firm throughout, but with more solid, irregular, pea-sized nodules scattered near the surface and in the depths. The mass is moderately sensitive to pressure. It is fixed to the underlying tissues. There are a few enlarged, tender lymphnodes in the right submaxillary triangle. The parotid duct is felt as a firm, rigid strand in the cheek. The mouth of the duct can be barely distinguished. It makes a tiny pale depression in the buccal mucous membrane; saliva does not escape when the parotid mass is compressed. The finest lacrymal probe cannot be introduced into the orifice of the duct.

The diagnosis of parotid sarcoma would have been concurred in were it not for the duct findings. The parotid swelling itself appeared absolutely typical. Slitting of the duct (in order to explore it) was suggested before sending the case to the wards.

Treatment and Course.—General anesthesia. The smallest probe could be passed into the very narrow, stiff-walled duct for about 1 cm. A tight stenosis was then met. With a little manipulation the probe was pushed through a stricture less than 1 cm. long and was then passed into the dilated duct beyond. The cicatricially stenosed part of the duct was slit open from the orifice; the result was a very wide opening leading to the dilated duct. Quantities of thick mucoid saliva escaped. The lining of the dilated part of the duct was then seen to be much thickened, congested, and edematous. A large probe could be introduced to the gland. It described a somewhat irregular course but met no other strictures. The wall of the duct felt very rigid.

Two weeks after operation the parotid tumor had diminished greatly in size and was much softer and more homogeneous in consistency. The only postoperative treatment was pressure made over the gland, at each visit to the clinic (resulting in profuse discharge of saliva from the duct). No visible swelling remained at the end of one month, but the gland was, as yet, firmer and more resistant to touch than the normal. The child disappeared from observation at that time, to return five weeks later with a recurrence of the parotid swelling (to about half the size of the original tumor) and of the stenosis of the duct orifice. The latter was again slit open under general anesthesia; the gland swelling promptly receded. Progressive dilatation of the buccal end of the duct was then practiced for several weeks. Instructions were given for the return of the child twice a month, for the passage of sounds. This was not done, and the patient was not seen again until two and a half months later. The duct mouth was then found partly closed and the parotid gland slightly enlarged. The duct was slit a third time, and there was the same prompt reduction in the size of the parotid. With dilatation by probes for a few weeks the duct has remained patent permanently. When last seen, in July, 1915 (about two years after operation), the patient was well and in excellent general condition. The orifice of the duct was slightly larger than

the normal, could be probed easily; normal-looking saliva escaped; no enlargement of the parotid gland was discernible.

CASE 2.—A girl 8 years old came under my observation in May, 1915, with a swelling in the right parotid region, of four months' duration. The mass increased in size rapidly in the first few weeks, more slowly thereafter. In the first two weeks there was slight fever, and considerable pain in the cheek. The latter was largely controlled by the application of hot poultices. Changes in secretion of saliva were not noted. The physician in charge stated that the parotid swelling was uniform at first, in every way identical with mumps; subsequently, however, the mass became irregularly nodular. There was never any discharge of pus into the mouth. The diagnosis of "mixed tumor" of the parotid had been made, and excision advised. The only suggestive feature in the previous history was that extensive wiring of the teeth to adjust the "bite" had been completed about two months before the onset of the parotid swelling.

The general examination was negative. There was no existing lesion and no evidence of a previous one in the buccal mucous membrane. The left parotid gland and duct were normal. The mucous membrane immediately around the orifice of the right duct was pale and firm to touch. The mouth of the duct was exceedingly small and evidently stenosed. The finest lacrymal probe was introduced with some difficulty. It traversed a very narrow, irregular course for some 2 cm., then suddenly entered the (apparently) dilated duct beyond, and went directly to the gland. The parotid gland was about the size and shape of an English walnut, slightly sensitive, rather firm and resistant to touch, with a number of shotty nodules scattered near the surface and in the depths. The mass was slightly moveable on the underlying tissues. Without the presence of the sound the course of the duct in the cheek could not be felt. (Compare with Case 1.)

The diagnosis of sialodochitis with duct stenosis was made, on the basis of the experiences in the former case. In order to avoid the postoperative recurrences of the stenosis excision of the sclerotic part of the duct was planned.

Treatment and Course.—Under local anesthesia the cicatricial tissue around the mouth of the duct was freed. With a probe in the duct as a guide the distal, stenosed end of the canal was isolated and removed with the tissue about the duct orifice. Immediately following the excision there was a profuse flow of glairy saliva mixed with thin watery fluid (cultures sterile). The remaining part of the duct could be probed readily, felt stiff and resistant, and was evidently dilated. A single cat-gut suture approximated the new orifice of the duct to the mucous membrane. Two sutures closed the remainder of the wound to within a short distance of that orifice.

The postoperative course was smooth. Saliva discharged freely from the new duct mouth, the parotid swelling steadily decreased. In three weeks the gland was of almost normal size and much softer in consistency; the nodules were also much softer as well as more indefinite. Two months after operation the gland was barely palpable, the nodules had disappeared, the discharge of saliva was free, the entire course of the duct could be readily probed, and there was no tendency to recurrence of stenosis. When seen recently (November, 1915, six months after operation) the child was quite well; a difference between the parotid glands was not discernible, the new duct orifice remained patent, probing it revealed no abnormalities.

CONCLUSIONS

1. Sialolithiasis in childhood cannot be termed the exceedingly rare, almost unknown condition it is presumed to be. The manifestations are more clean-cut and evident in children than in adults, the diagnosis

can be made more readily, the surgical treatment is simple and efficacious. The salivary duct should be probed in every instance of enlargement of a salivary gland in a child when a definite cause for the enlargement cannot be ascertained.

2. There is a hitherto undescribed form of sialodochitis of Stenson's duct in children, secondary to inflammation of unknown origin, leading to an enlargement of the parotid gland that can be readily mistaken for sarcoma or mixed tumor. The gland is considerably increased in size, firm, nodular, adherent; the orifice and buccal end of the duct are embedded in stenosing cicatricial tissue. There is a tendency to repeated recurrences of the parotid swelling after slitting the mouth of the duct, but cure follows promptly the excision of the diseased end of the duct.

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THE POSTOPERATIVE MANAGEMENT OF PYLORIC STENOSIS *

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The exhaustive work and intensive studies made in the last decade on the subject of pyloric stenosis has been productive of an almost complete understanding of the disease. The age and sex incidence is typical, the symptom complex is unusually constant, the differential diagnosis affords few difficulties and the treatment is limited practically to one procedure. There is a growing conviction that early surgical intervention is to be advised, except in a very small percentage of the cases. The etiology of the disease alone is shrouded in obscurity. Dr. Holt's paper, read before the New York Academy of Medicine in April, 1914, covered the subject from a medical point of view, and to Dr. William A. Downes should be given credit for the most complete discussion of the surgical treatment, his latest paper having been recently read before the Southern Surgical and Gynecological Congress at Cincinnati. The opportunity at the Babies' Hospital for the study of this disease may be understood when one considers the fact that in the last four years there have been admitted to the wards of the hospital seventy-five cases of true pyloric stenosis.

To the average surgeon who is called on to relieve the condition, the operation itself has few terrors, but to him, and to the practicing physician who has not been fortunate enough to see these cases, the postoperative treatment is full of difficulties. It is true that in the majority the convalescence after operation is attended by few mishaps, and this is natural when one considers the fact that there has been no impairment of the digestive functions other than that caused by starvation. A certain proportion of the patients, however, turn out to be difficult feeding problems, in spite of the fact that every facility is at hand for their proper care.

The object of this paper is to set forth, in as comprehensive a manner as possible, the usual postoperative management of these children as it has been practiced in the Babies' Hospital, and to draw attention

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to the difficulties which are likely to be encountered. The study is based on the personal observation of fifty children who were operated on in this hospital during the last two years.

Since the postoperative results are dependent to no little extent on the preoperative condition of the patient, a discussion of the methods employed to improve this condition is not out of place.

PREPARATION OF PATIENT

The maintenance of the body temperature is of paramount importance; indeed the outcome of the case may hinge on the amount of care given to this detail. The metabolic processes of these children have been in abeyance, and their subcutaneous fat has been depleted by several weeks of starvation. The facility with which they develop a subnormal temperature may be readily understood; and it has been our experience that a sudden loss of body heat has, in some instances, been the undoubted cause of collapse occurring a few hours later.

The greatest danger is in the exposure incident to the operation, and to minimize this it is advisable to encase the infant's legs and arms in nonabsorbent cotton. Layers of this are covered on one side by a sheet of gauze, and the pads thus formed are folded into the shape of cylinders closed at one end, and can be drawn up over the legs and arms. Under the pad on the operating table is placed a hot water bag which fits into the small of the back and serves the double purpose of supplying warmth and keeping the site of the operation well elevated. It can be easily slipped out, if advisable, while the abdominal wound is being closed. The temperature of the operating room should be between 75 and 80 F.

The removal from the infant's stomach, by gastric lavage, of food residue and gas accumulation is the next most important preoperative measure. It should be done just before the child is taken to the operating room. Colon irrigation is unnecessary, as the intestinal coils are as a rule empty and collapsed.

Another consideration is the administration of stimulants before operation. These should be withheld except in a very small proportion of the cases. Hypodermoclysis of normal saline may be necessary in the severely dehydrated and prostrated patients, but its use before operation is open to several objections: (1) its administration entails a certain amount of exposure; (2) the tumor formed on the back may not be absorbed in time, and therefore increases the difficulties of maintaining the proper position of the child while on the operating table; and (3) not infrequently the subcutaneous fluid works around to the ventral surface of the body and encroaches on the site of operation. It is strongly advised, therefore, to postpone its use until after the operation when its beneficial effects are much more marked.

POSTOPERATIVE MEASURES

The care of the child after operation depends to some extent on the nature of the operation performed. In this series there were thirteen gastro-enterostomies and thirty-seven plastic or Rammstedt operations, of which all but two were performed by Dr. William A. Downes. The plastic operation has many advantages over the gastro-enterostomy, and it has been one of choice in the last thirty-four cases. It is more rapid, is simpler, entails less handling of the viscera, and consequently less shock, and ensures a smoother convalescence.

Maintenance of Body Heat.—In the postoperative management the maintenance of the body temperature is, as before, of the utmost importance. The infant is wrapped in a warm blanket, or cotton jacket, and the bed is well equipped with hot water bottles.

Position.—For the first hour or two the head of the bed should be lowered. This rule was adopted in the hospital when one child, while still under the influence of the anesthetic, aspirated some mucus into its larynx, after being taken to the ward, and was resuscitated only with great difficulty. After nourishment has been commenced the head of the bed may be raised and from this time on the infant is kept in a semi-erect position. This elevation assists in the emptying of the stomach, especially in the gastro-enterostomy cases, and at the same time permits the escape of gas through the mouth.

Stimulation.—The use of excessive hypodermic stimulation after operation is to be deprecated; only one measure, namely, hypodermoclysis of normal saline or of glucose solution, is always indicated, and this may be safely used as a routine practice. The amount given depends on the size of the child, but 120 c.c. or 240 c.c. are the amounts commonly used. As its administration involves exposure of the child it is important, especially in the emaciated infant, to make sure that the temperature is not subnormal. The results obtained by the use of enteroclysis are so uncertain that its employment cannot be recommended.

Of the other stimulants, epinephrin, subcutaneously, is the most satisfactory because of the rapidity of its action. Caffein and atropin, hypodermically, are sometimes valuable, and by mouth dilute whiskey or brandy. The latter cannot be given, however, until the pharyngeal reflex has returned, but it is then of unquestionable value. At times it has seemed as though merely the act of sucking from a nipple or a medicine dropper has had a stimulating effect.

It is a matter of constant surprise how well these infants withstand the shock of the operation. Frequently they look in better condition an hour afterward than they did before, and it is possible that this is due to ether stimulation. For the first half hour the child's color is,

not infrequently, poor, the pulse may be so small that its detection is difficult and the respirations are often shallow and sobbing. These signs should not cause undue alarm as they usually disappear quickly, but the child should be very closely watched for the first hour.

The value of transfusion as a stimulant is very questionable. Of the fifty cases in this series, six were transfused. In one there had been a specific indication in the form of a postoperative hemorrhage from the wound, and the beneficial result of the blood injection was immediate and impressive. In two others, who collapsed shortly after operation, the transfusion was performed solely as a stimulating measure, but had not the slightest effect. The fourth patient was one who, following operation, made a rapid convalescence for the first week, but then developed an otitis media and a severe cellulitis of the buttocks. The digestion became impaired and the weight gradually dropped. A blood transfusion was followed by a steady rise in weight and by a distinct improvement in the infectious process. The other two transfusions were performed on patients who, after operation, developed typical marasmus. One recovered and one died, but in neither instance could any beneficial effect, except a very transitory one, be attributed to the transfusion. The conclusion that the use of transfusion is of little value as a stimulating measure may be open to some criticism in view of the small number of cases described, but the same conclusion has been reached in this hospital by the study of the results obtained by transfusion in prostrated marasmus and gastro-enteritis cases.

Temperature Reaction.—A postoperative rise in temperature is to be expected in nearly all the cases. Several factors are concerned in its production: (1) the reaction from the shock of the operation; (2) the administration of hypodermoclysis and other stimulation; (3) employment of artificial heat. The height of the reaction is usually reached in from four to eighteen hours, and then gradually returns to normal during the first thirty-six hours.

The operation of gastro-enterostomy is followed by a higher and more sustained temperature than is the plastic operation, the average highest figure in eleven cases of the former variety being 102, and in twenty-six of the latter variety 101.4. The average duration of the fever after gastro-enterostomy was thirty-three and three-tenths hours, and after the plastic operation only eighteen hours. The difference in the length of the two operations, and in the amount of handling of the viscera is possibly sufficient to explain this.

A pyrexia that persists for more than three days, or one that unexpectedly occurs after the first reactionary fever has subsided, should be investigated, as it usually indicates some complication.

No antipyretic measures are needed for this reactionary temperature, except that care should be taken not to use excessive artificial heat.

Feeding.—This is the most important feature of the postoperative care of these infants; a slight error in judgment may precipitate a gastro-intestinal upset that is very difficult to control. It is impossible to feed all the children by the same set rule, but a general routine is of value and is applicable to the majority of cases. The aim should be, as soon as possible after operation, to start nourishment in a concentrated and readily digestible form. For this purpose there is no food that can take the place of breast milk, and every effort should be made to procure enough to tide the patient over the first week at least.

The routine at the Babies' Hospital has changed to some extent in the last two years. In the early cases of this series, which were nearly all gastro-enterostomies, nourishment in the form of dilute breast milk was begun four hours after operation; water was given either one hour before this time or one hour afterward. With the advent of the plastic operation, however, it was thought that the feeding might be begun with safety at an earlier period. As this theory proved, after trial, to be correct, the following general routine was gradually evolved:

The patient is given, an hour after operation, providing the recovery from the anesthetic has been complete, 16 c.c. of water, and an hour later 12 c.c. of breast milk mixed with 4 c.c. of water. It may be necessary at first to use a medicine dropper for the administration. The breast milk is repeated every three hours, eight feedings a day, and is alternated with the water. Both are gradually increased so that twenty-four hours after operation 16 to 24 c.c. of undiluted breast milk is being given every three hours and a similar amount of water between feedings. At the end of forty-eight hours the child is usually taking 20 to 30 c.c., and at the end of seventy-two hours 30 to 45 c.c. at a feeding. The administration of water by mouth during the first three or four days is of the greatest importance. The time required to increase the milk to meet the caloric requirements of the child has been on an average five days; in small babies three days may be sufficient, and in the well nourished as much as eight to ten days.

Nursing.—Of the fifty children, thirty-four had been nursed up to admission or shortly before, and the mothers' breasts were still secreting. As the child's subsequent condition depends on the amount of breast milk that is available, every effort should be made to stimulate the failing supply. There is no better way of accomplishing this than by giving the mother a vigorous baby to nurse four or five times a day. If this is not possible a breast pump should be used.

The mother of one child in this series had not nursed her baby for eleven days before admission, and her breasts appeared to be empty.

The stimulation of nursing coupled with attention to her general health was sufficient to so restore the flow of milk that she was prepared to nurse her own baby in ten days. She was well rewarded for her trouble, since the infant during the next seven months gained fifteen pounds.

It is wise not to defer putting the baby to the breast longer than one week after operation, or when the feeding from the bottle has been increased to about 60 c.c. This is usually on the sixth or seventh day. The nursing must be carefully supervised for the next week, the amount taken at each time being measured by weighing the baby before and after. If the quantities obtained are too small, the nursing may be supplemented by a modified milk mixture.

If it is impossible to reestablish the mother's secretion, there are two alternatives open: (1) a wet nurse, if the parents can afford it; (2) the use of modifications of cow's milk. The latter may be gradually substituted for the breast milk, beginning the substitution about the tenth or twelfth day after operation.

Bathing.—In the well-nourished children a sponge bath may be given every day until the abdominal wound is completely healed and the dressing discarded. In the poorly nourished or emaciated infants an oil rub is to be preferred until a substantial gain in weight has been recorded or until the danger of the occurrence of subnormal temperature is passed.

Vomiting.—This symptom, although it is to be expected in a certain degree in a large proportion of the patients after operation, is in some cases frequent and troublesome. It is encountered after a gastro-enterostomy more commonly than after the Rammstedt operation. Twelve gastro-enterostomy patients, who survived one week or more after the operation, vomited in the first week small amounts (4 c.c. or less) an average of 6.3 times, and large amounts 4.5 times. Following twenty-five plastic operations the average number of vomitings of small amounts was only four, and of large amounts two during the same period. Vomiting persisted during the second week in 55 per cent. of the gastro-enterostomy cases, but in only 21 per cent. of the Rammstedt variety.

The more common exciting causes of the vomiting are as follows:

1. Distention due to accumulation of gas in either the stomach or intestines.
2. Defects in the operation, such as faulty adjustment of the jejunum and stomach, or incomplete severance of the constricting muscle fibers by the plastic operation.
3. A too rapid increase of the feeding.
4. The occurrence of complications, especially general peritonitis.

Of these causes distention due to gas accumulation is by far the most frequent. If it is mainly intestinal, a colon irrigation, repeated as often as is necessary, is all that is required for relief. When the accumulation is in the stomach the head of the bed should be elevated and the child frequently raised to the upright position, to allow the free escape of the gas; in the patients who do not respond to these measures it is well to pass a soft rubber catheter into the stomach before each feeding. Lavage may be employed if the vomiting is persistent, but its use in the first two or three days after the operation of gastro-enterostomy entails not a little risk.

In discussing the causes of vomiting, which are directly related to the operation itself, it should be mentioned that in the first nineteen of the Rammstedt cases an additional incision was made in the anterior wall of the stomach through which a large sound was passed into the pylorus to ensure the patency of this passage. These patients as the result of the extra trauma to the mucous membrane, showed a greater tendency to postoperative vomiting than did the patients on whom the simple muscle-splitting operation was performed. There were in addition three children whose pyloric mucous membrane was accidentally ruptured during the division of the circular muscle fibers. The defect was closed with catgut sutures, but there remained apparently a partial occlusion of the lumen, since these patients vomited excessively for two to three weeks. All eventually made good recoveries.

Persistent vomiting, the absence of fecal movements, and the demonstration of retention of food in the stomach are very suggestive of an operative defect. The diagnosis, however, is very difficult and frequently in such cases no cause for the vomiting is discovered at necropsy. In one case was found, however, a dilatation of the proximal loop, between the pylorus and gastro-enterostomy opening, in which quantities of milk had apparently collected only to be regurgitated periodically into the stomach. Another child who vomited an average of three times a day for three weeks was found at necropsy to have a stomach the capacity of which was probably not more than 30 c.c.

The history of another case serves to illustrate a cause of persistent vomiting which, though unusual, should be kept in mind. The patient, following a simple Rammstedt operation, made uneventful progress until the third day after operation, when vomiting in small quantities commenced and gradually increased in severity. The food was reduced on two occasions from 75 c.c. to 60 c.c. with a slight amelioration of the symptoms. There were one or two fecal stools of moderate size in the twenty-four hours, but an estimation of the retention in the stomach showed that only one-half or one-third of the food was entering the intestines. It was thought the relief of the pyloric constriction had not been complete, and it was not until lavage was

commenced that the true cause of the vomiting was revealed. The stomach contained an abundance of exceedingly thick, tenacious mucus which was removed only with great difficulty through the lavage tube. This mucus had evidently accumulated in the pyloric canal occluding the lumen. With the employment of frequent washings over a period of eight days the vomiting ceased and the child made a good recovery.

Stools.—Repeated fecal evacuations are usually not seen during the first twenty-four hours. At the end of this period, therefore, it is well to give a teaspoonful of castor oil to stimulate peristalsis and remove mucus and gas. The first few stools are usually loose and green in color (or meconium-like if there has been any bleeding into the stomach). Normal breast milk stools are not seen as a rule until the fourth day after operation. After the effect of the castor oil has subsided the child should have from one to three stools a day; not infrequently, however, a diarrhea occurs. This symptom is encountered to a greater degree after a gastro-enterostomy than after the muscle-splitting procedure and constitutes one of the most serious objections to this type of operation, as viewed from the standpoint of the postoperative management. Over 50 per cent. of the patients who had a gastro-enterostomy performed developed a troublesome diarrhea, but this symptom was a feature of only 8 per cent. of the Rammstedt cases.

A too rapid increase in food, especially in those children who have been vomiting for several weeks prior to operation, is very apt to produce loose frequent stools.

The measures usually employed for the relief of acute intestinal disturbances are applicable to this condition: (1) reduction in the amount of food; (2) dilution of the food; (3) reduction of the carbohydrates, best accomplished by substituting three or four feedings of protein milk for the breast milk; (4) use of medication, such as mixtures of bismuth and paregoric.

It should be mentioned in this connection that we have come to recognize a certain group of cases showing a fairly characteristic symptom complex, namely, loss of appetite, which is a danger signal never to be disregarded, drowsiness, subcutaneous edema, and frequent loose fermentative stools. Since improvement follows a reduction of the carbohydrate content of the food, by the administration for instance of protein milk, it is rational to assume that the cause of the upset was a carbohydrate intolerance, acquired, perhaps, during the weeks of starvation previous to operation.

Urine.—Before operation the urine is usually small in amount and concentrated. In forty-two cases in which the parents' observations were reliable, a diminution or concentration was noted in twenty-six,

or 62 per cent. With the administration of water following the operation there occurs a marked increase in the output of urine. It is impossible to be sure that this concentration is never injurious; it is certainly infrequently so.

One patient in this series whose symptoms had persisted for over four weeks before admission, gave a history of having passed small amounts of concentrated urine during the previous two or three days. The child was operated on the evening of admission. Toward the end of the first twenty-four hours vomiting, fever and repeated convulsions occurred, which persisted up to the time of death four days later. During this period the urine was scanty and was found to contain, on examination, a large amount of albumin and a few casts. At necropsy a severe grade of acute exudative nephritis was discovered. There was no obvious explanation for an occurrence of the nephritis other than an irritation of the kidney by a highly concentrated urine.

Weight.—The average weight of all cases on the day of operation was 6.3 pounds. Of those patients who eventually recovered twenty showed an average initial loss in weight following operation of 3.5 ounces, the low weight being reached, on an average, the sixth day after operation. In thirteen of the cases there was no initial loss in weight. Of all the patients who recovered the average gain per diem, estimated from the low weight or operation weight, was more than 0.6 ounces.

Care of the Wound.—The dressing at operation should consist of a narrow fold of sterile gauze, which just covers the incision and is held in place by adhesive strapping; there is seldom any indication to disturb it for the next four or five days. A binder should not be used. The advantage in using a small dressing is that the least hemorrhage can be readily detected and controlled. The stitches may be removed on the sixth to the eleventh day, depending on the condition of the wound, and after this a protective pad of gauze is all that is required.

Prognosis.—The prognosis in any given case depends on the duration of the disease, the preoperative condition of the child, the nature of the operation performed and the experience of the surgeon. Of the fifty cases in this collection fourteen died—a mortality of 28 per cent. There were thirty-seven Rammstedt operations with a mortality of 27 per cent., and thirteen gastro-enterostomy operations with a mortality of 30 per cent. Eight of the children who died were moribund or collapsed on admission, and in these cases the average duration of the disease before operation was seven weeks.

Fifty per cent. of the deaths occurred in the first thirty-six hours after operation, so that, until the infant has passed through this danger period, the prognosis should be very guarded. After five days

of uneventful progress the parents may be reassured as to the ultimate outcome, since serious complications, such as peritonitis or hemorrhage, are unlikely to develop later.

Causes of Death.—In only six of the fourteen fatal cases could the cause of death be definitely ascertained. One died as the result of hemorrhage into the abdominal cavity from the pyloric incision, two from general peritonitis, another from acute nephritis, and in two more death was the result of two or three weeks of persistent vomiting. The necropsy findings in the last two have already been mentioned in the section dealing with postoperative vomiting.

Of the remaining eight children, two died as the result of starvation caused by an uncontrollable gastro-intestinal upset. A necropsy in each instance revealed no pathologic change in any of the organs. Death in the other six cases was attributed to postoperative shock, but this explanation is not entirely adequate. Four, at least, showed no evidence of shock until the end of the first twenty-four hours, when collapse occurred unexpectedly. These children were all of one type, the points of resemblance being (1) a white, wrinkled, almost transparent skin, with a marked reduction of tissue turgor and other evidences of a rapid loss in weight, (2) a distinct tendency to subnormal temperature, (3) prostration to a greater or lesser degree.

It is of some interest to note that of the fourteen deaths, only three could be ascribed to medical causes; the remainder were surgical in nature.

Subsequent Course.—Of the thirty-six infants discharged in good condition, four died from a variety of causes, none of which were directly associated with the operation; the deaths occurred two weeks after discharge in two instances, and two months after discharge in the others. Two children were lost sight of, and of the remainder ten were followed for one or two years after discharge, thirteen for six months to one year, and seven for less than six months.

On the majority accurate weekly or monthly weights were obtained from the parents, and in every instance consistent gains in weight were reported. Ten children, whose weight was accurately recorded for at least nine months after leaving the hospital, gained on an average 1.3 pounds a month during this period. Eleven cases, followed for six months, at least, showed an average gain of 1.6 pounds a month. Some of the gains in weight were astonishing; two children, for instance, gained 1.5 ounces a day for four months, and several others averaged an ounce a day. The degree of improvement is naturally more striking if the baby is on the breast than it is if cow's milk is used, but in either case progress is very satisfactory.

The danger of a recurrence of the symptoms is practically negligible; a poorly executed gastro-enterostomy may be the source of trouble at a later date, but there has never been an authentic record published of a recurrence of symptoms following the Rammstedt operation.

The accompanying chart is that of a fairly typical case, and is intended to illustrate the most important incidents and treatment in the postoperative care. The solid line, which represents the weight, also represents, by striking out the last cipher, the caloric requirements of the child estimated on the basis of 100 calories per kilo. The dotted line represents the caloric intake. The steady gain in weight is interesting in view of the fact that the infant was fed its full caloric requirements only on one day—the seventh day following the operation.

I am greatly indebted to Dr. L. Emmett Holt, on whose service in the hospital these cases were observed, for permission to publish this report and also for his help in its preparation.

THE PRACTICAL VALUE OF THE GUINEA-PIG TEST FOR THE VIRULENCE OF DIPHTHERIA BACILLI

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Owing to the frequency of diphtheria and the comparative ease of making bacteriologic examinations in this disease, the laboratory has been freely used as an aid in its diagnosis and management, so that the bacteriology may be considered one of the best developed subjects in the domain of bacteriology.

The morphologic, biologic and tinctorial qualities of diphtheria bacilli are so distinctive that with comparatively little experience they are readily detected in properly made cultures, and if diphtheria bacilli were to be found on mucous membranes only in diphtheria and disappeared in a reasonable length of time after the clinical evidences of infection had disappeared, nothing would be simpler or more satisfactory than the bacteriologic diagnosis of the majority of these infections.

From a practical standpoint, however, the bacteriologic diagnosis of diphtheria is greatly complicated by reason of the fact that many persons harbor diphtheria-like bacilli in the mucous membranes, particularly of the nose and throat, that are apparently harmless and compatible with normal health. In the presence of inflammatory changes in these parts, or following direct exposures to a known case of diphtheria, the presence of these "carrier" bacilli greatly complicates the situation when it is necessary to determine whether or not a condition of infection with diphtheria bacilli may be present.

Likewise, following an attack of diphtheria, the bacilli may persist for long periods on the mucous membranes even though the patient is in all respects restored to health; most physicians have encountered these cases in private and hospital practice when prolonged, expen-

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sive and tiresome quarantine was necessary because of the possible danger of transmitting virulent bacilli to others, until repeated cultures showed the patient to be, temporarily at least, free of diphtheria bacilli.

We now know that these "carrier" cases, both the convalescent and the person who has never had clinical diphtheria, may carry either virulent and disease-producing bacilli or nonvirulent bacilli; in not a few instances both virulent and nonvirulent forms are present on the same mucous membrane. In practice it would be simplicity itself to prolong the quarantine of all convalescents until repeated cultures show the absence of diphtheria bacilli, and likewise to quarantine all healthy "carriers" who have been in contact with a person with clinical diphtheria. These procedures, however, may bring great hardship to a person or family by reason of prolonged isolation and detention; the attending physician may regard lengthy quarantine as a reflection on his ability and a reversal of his opinion regarding the condition of his patient, and he may in this manner suffer in professional reputation.

It is readily understood, therefore, that some practical and reasonably sure means of differentiating virulent from nonvirulent diphtheria bacilli is highly desirable. The test should be one that is easily applied; that is sufficiently delicate to detect the potential harmfulness of bacilli with low grade virulence and it should give the result as quickly as possible.

Before any test, however delicate and accurate it may be, can be accepted as sufficiently safe in practical work to regard a "carrier" as free of danger to himself and others on its evidence, several important questions must be answered with reasonable positiveness: 1. Can bacilli that are without disease-producing powers according to our tests resume virulence and induce disease? 2. May not bacilli of low pathogenicity produce an infection in a second individual of low resistance while causing no apparent harm to the carrier? 3. May not virulent bacilli gradually lose virulence and later resume full pathogenic powers under conditions over which we have no control?

1. Without detailing the large amount of research work by many investigators which these questions have rendered necessary, we may state that the great weight of experimental evidence is to the effect that diphtheria bacilli which have proved nonvirulent with every test, remain so indefinitely despite prolonged efforts to give them even feeble pathogenic powers. A few bacteriologists claim to have successfully accomplished this feat, but their work has not been generally confirmed.

2. It is entirely different, however, with bacilli of low pathogenicity; with these, passage through animals or from throat to throat among men, may readily enough restore a high degree of pathogenicity and for this reason any test for the virulence of diphtheria bacilli must be

one sufficiently delicate to detect the weak pathogenic powers of such cultures. It is reasonable to suppose, and clinical experience supports the contention, that a bacillus of low pathogenicity and apparently harmless to its host, may be capable of harm in a second individual.

3. The third question is more difficult to answer. Many observers have noted that diphtheria bacilli retain their virulence until they disappear, regardless of the length of their stay. We have found this to be true in not a few instances, as with patients fully recovered from diphtheria who continue to harbor virulent bacilli for prolonged periods of time. These instances are readily understood when it is remembered that diphtheria bacilli may retain their virulence for years under the more unfavorable conditions of artificial culture mediums. But in our experience we have also reason to believe that after a time, the minimum being not less than two weeks, a proportion of bacilli prove non-virulent when tested by animal inoculation. Whether or not they regain virulence when passed from throat to throat is the important question, difficult to answer because the disease may be spread in such a varied and confusing manner, but in a considerable experience with these cases we have no direct evidence that this occurs. Most physicians depend on two or three consecutive negative cultures before discharging a patient as cured, but when one stops to consider the fallacies of this method and the goodly proportion of those who escape still carrying their bacilli, as shown by a more extended series of cultures, it is a question whether or not a good virulence test is not to be preferred.

Further than this, we have reason to believe that in some instances the prolonged number of positive cultures following diphtheria are due to the presence of harmless diphtheria-like bacilli of "carriers" that had no connection with the attack of clinical diphtheria. They were present before the attack of diphtheria and are likely to remain for an indefinite time afterward. At first they may be overgrown by the disease-producing bacilli or overlooked in cultures, but as the latter disappear the nonpathogens become prominent again and yield a formidable line of positive cultures.

It is clearly apparent, therefore, that some means of differentiating between pathogenic and nonpathogenic diphtheria bacilli must be available if the diagnosis and control of diphtheria is to be based on bacteriologic examination. Differentiation according to morphology is not usually possible or sufficiently accurate, although it is well known that the granular or beaded and barred types are more likely to be virulent than the solid types; likewise, biologic characters do not serve in this capacity; a rich creamy white growth is more frequently found with nonvirulent, solid types, while the granular, virulent bacilli grow less luxuriantly, but these characteristics are not definite. Acid production

with various sugars is likewise irregular and indefinite, although the granular, virulent types generally produce acids with dextrose and dextrin, while the nonvirulent Hoffman's bacillus produces no acid at all. Between these extremes cultures of various degrees are encountered, and indeed the variations in virulence among diphtheria bacilli have practically no parallel among other pathogenic bacteria.

The animal inoculation test therefore remains the only means now known for determining the virulence of a culture of diphtheria bacilli. To be reliable and satisfactory as a practical measure, an animal inoculation test must fulfill certain fundamental requirements:

1. It must be specific and sufficiently delicate to detect the pathogenicity of bacilli of low virulence on the basis that such bacilli may be capable of harm when transferred to the mucous membranes of persons less susceptible than the carrier.
2. The test must be simple and easily interpreted; also economical and possible of completion in as short a time as consistent with accuracy.

Aside from these requisites certain technical factors, which need not be detailed in this communication, must be considered in order to obtain the best results.

Experimental work has shown that the tissues of the guinea-pig are best adapted for conducting virulence tests, in addition to the general adaptability of this animal for such laboratory purposes.

While there is no parallel between the mechanism of human infections and animal inoculation tests, yet experience has shown that a micro-organism found nonvirulent in a carefully conducted animal inoculation test may be regarded as harmless to human beings, although the final and decisive test is actual transference of these bacilli from throat to throat; and since diphtheria is so frequently spread in such a varied and confusing manner, absolute statements are not justifiable. As pointed out in this paper, our experience has taught us that a properly conducted virulence test may be regarded as reliable and a safe method, and much to be preferred in general, to two, or even three, consecutive negative cultures, in deciding the question of quarantine of a person harboring diphtheria bacilli over a long period of time.

In the Philadelphia Hospital for Contagious Diseases virulence tests have been conducted routinely for the past six years on cases showing positive cultures after two or three weeks' detention in the hospital, and in all cases showing diphtheria or diphtheria-like bacilli but with the diagnosis still more or less in doubt. In this class of cases are included moist or dirty noses, discharging ears or wounds, and inflamed throats showing no exudate.

Reports on the technic and results of these tests have been made by Weston and Kolmer¹ and by Kolmer.²

During the past two years Kolmer and Moshage³ have made a study of various methods for determining the virulence of diphtheria bacilli, with the result that from the standpoints of delicacy and comparatively brief time required for a virulence test the subcutaneous injection into 250 to 300 gm. pigs of 4 c.c. of twenty-four-hour Loeffler culture removed with 10 c.c. of normal salt solution, yielded the best results (Table 1).

TABLE 1.—A SUMMARY OF RESULTS REGARDING THE VIRULENCE OF DIPHTHERIA BACILLI AS DETERMINED BY VARIOUS METHODS

Total Examined	Culture Medium	Hours Incubation	Route of Injection	Per Cent. Positive Results	Culture Medium	Hours Incubation	Route of Injection	Per Cent. Positive Results
37	Pl. Dext. broth	72	Subcut.	86.5	Pl. Dext. broth	72	Intracut...	64.9
28	Pl. Dext. broth	72	Subcut.	65.1	Loeffler.....	24	Subcut. ...	60.6
8	Serum Dext. broth	72	Subcut.	62.5	Loeffler.....	24	Subcut. ...	62.5
27	Pl. Dext. broth	72	Subcut.	74.0	Pl. Dext. broth	24	Intraperit.	63.0
8	Serum Dext. broth	72	Subcut.	75.0	Serum Dext. broth	24	Intraperit.	75.0
27	Pl. Dext. broth	72	Subcut.	63.0	Pl. Dext. broth	72	Intraperit.	55.5
9	Pl. Dext. broth	72	Subcut.	45.5	Pl. Dext. broth	9 days	Subcut. ...	66.6
8	Pl. Dext. broth	72	Subcut.	50.0	Serum Dext. broth	72	Subcut. ...	75.0

The subcutaneous injection of seventy-two-hour serum dextrose broth cultures in doses corresponding to the weights of the animals yielded good results but required more time for the conduct of the test; likewise the intraperitoneal injection of twenty-four-hour serum dextrose broth cultures yielded good results and had the merit of showing the result in less time than the subcutaneous method. The intracutaneous injection of 0.1 c.c. of seventy-two-hour plain dextrose broth cultures was found inferior to the subcutaneous injection of larger doses, as 1.3 c.c. for a 260 gm. pig; furthermore, the results of the intracutaneous injection were more difficult to read, especially with bacilli of a low degree of virulence. For further details and results we refer the reader to the paper mentioned.

During the past four years 1,054 virulence tests have been conducted, and the object of this paper is to report on the results observed and their practical value in the management of diphtheria.

1. Weston, P. G., and Kolmer, J. A.: Jour. Infect. Dis., 1911, viii, 295.

2. Kolmer, J. A.: Jour. Infect. Dis., 1912, xi, 56.

3. Kolmer, J. A., and Moshage, E. L.: Jour. Infect. Dis. (To be published).

TECHNIC

The technic employed in conducting the tests herein reported may be briefly described as follows:

1. Isolation of the bacilli by the "streak" method on plates of Loeffler's blood serum medium.

2. The inoculation of tubes of plain 0.2 per cent. dextrose broth with a reaction of +0.8 with several different colonies so as to make more certain that the cultures will contain virulent bacilli if the plates contain colonies of virulent and nonvirulent bacilli.

3. Cultivation of the broth cultures at 35 to 37 C. for seventy-two hours (tubes in a slanting position so that the bacilli may receive the maximum of oxygen, which favors toxin production).

4. The examination of the broth culture for purity, followed by the subcutaneous injection in the median abdominal line of a 250 to 300 gm. pig of a dose of unfiltered culture corresponding to 0.5 per cent. of the weight of the animal expressed in cubic centimeters. The total amount injected is brought up to 4 c.c. by the addition of sterile normal salt solution in order to equalize pressure and absorption.

5. The animal is observed for at least four days for evidences of local inflammatory edema and general toxemia. If death occurs the animal is necropsied for the typical changes of diphtheritic infection, namely, local inflammatory edema, congestion of the suprarenal glands, pulmonary changes, etc. Cultures are prepared from the site of injection and the internal organs.

6. Frequently and especially when in doubt of a result and with positive or presumably virulent cultures, a second pig is injected with the same amount of culture, plus 1 c.c. of a 500-unit antitoxin serum.

7. Local edema and evidences of toxemia are regarded as indicating virulence of a culture, even though the animal does not succumb in the usual period of four days.

As will be noted, unfiltered cultures are used entirely because the soluble toxins secured by filtration are but one element of the pathogenicity of a culture, and in virulence tests it is desirable to include a test of all possible pathogenic agents.

Types of Bacilli.—In classifying the cultures submitted to the virulence test the types were recorded after the classification of Westbrook, Wilson and McDaniel. For the sake of brevity all the types found in the cultures are not recorded. For example, in a given culture of granular bacilli Types A, B and C may be found, although if one predominates, the culture is recorded according to that type. The cultures for the virulence test were recorded as follows:

A. Granular bacilli, A, B, C and D—mostly C.

B. Barred bacilli, A₁, B₁, C₁ and D₁—mostly B₁.

C. Solid bacilli:

Long solid—A₂, B₂ and C₂—mostly C₂.

Short solid—D₂ and E₂—mostly D₂.

RESULTS

The results of 1,054 tests conducted after the method outlined with granular, barred and solid bacilli from the throat, nose, ear and other mucous membranes, are shown in Tables 2, 3, 4 and 5.

TABLE 2.—RESULTS OF VIRULENCE TESTS WITH 551 THROAT CULTURES OF DIPHThERIA BACILLI

Types	Total	Results		Per Cent. Positive
		+	—	
Granular (mostly C).....	202	141	61	69.8
Barred (mostly B ₁).....	17	10	7	58.8
Long solid (mostly C ₂).....	311	144	167	46.3
Short solid (mostly D ₂).....	21	21	20	4.7

TABLE 3.—RESULTS OF VIRULENCE TESTS WITH 261 NOSE CULTURES OF DIPHThERIA BACILLI

Types	Total	Results		Per Cent. Positive
		+	—	
Granular (mostly C).....	102	74	28	72.5
Barred (mostly B ₁).....	7	5	2	71.4
Long solid (mostly C ₂).....	129	52	79	40.3
Short solid (mostly D ₂).....	23	0	23	0

TABLE 4.—RESULTS OF VIRULENCE TESTS WITH 217 EAR CULTURES OF DIPHThERIA BACILLI

Types	Total	Results		Per Cent. Positive
		+	—	
Granular (mostly C).....	105	70	35	66.6
Barred (mostly B ₁).....	6	5	1	83.1
Long solid (mostly C ₂).....	73	31	42	42.4
Short solid (mostly D ₂).....	38	1	32	3.0

TABLE 5.—RESULTS OF VIRULENCE TESTS WITH 25 MISCELLANEOUS CULTURES OF DIPHThERIA BACILLI

Sources	Types	Total	Results		Per Cent. Positive
			+	—	
Penis.....	Long and short solids.....	6	0	6	0
Vagina.....	Long solids.....	6	0	6	0
Eye (normal).....	Long solids.....	4	0	4	0
Gallbladder.....	Long solids.....	1	0	1	0
Skin.....	Long and short solids.....	8	0	8	0

Table 6 is a summary of the virulence of the different types of bacilli from the different sources.

TABLE 6.—COMPARATIVE VIRULENCE OF THE DIFFERENT TYPES OF BACILLI FROM DIFFERENT SOURCES

Type of Bacilli	Percentage of Positive Results of Cultures			
	From Throat	From Nose	From Ear	From Various Other Sources
Granular (mostly O).....	69.8	72.5	66.6	None tested.
Barred (mostly B ₁).....	58.8	71.4	88.2	None tested.
Long solid (mostly O ₂).....	46.8	40.3	42.4	0
Short solid (mostly D ₂).....	4.7	0	8.0	0

An examination of these tables shows the following:

1. The granular and barred types of bacilli give the highest percentage of positive tests. In clinical diphtheria they are almost invariably virulent for guinea-pigs. No matter how long they persist in the throat after recovery, they should be regarded as dangerous until proved otherwise. Of all types they are most likely to retain their virulence.

2. The value of animal inoculation tests is especially appreciable when dealing with solid types of bacilli. The longer types are more likely to retain virulence than the shorter varieties. Both, however, may be descendents of the "carrier" bacillus rather than of the bacillus producing the clinical evidences of the disease.

3. The short solid types of bacilli are especially common in the nose in the absence of clinical diphtheria. In a small percentage of cases these bacilli may be truly pathogenic but the majority of cultures are found without virulence when tested by animal inoculation.

4. The long solid types of bacilli, so frequently found in otitis media, are in the majority of cases nonvirulent.

5. Animal inoculation tests have a special field of usefulness in testing the solid types for virulence when they persist in the tissues over a long period of time or when found after contact with "carrier" cases.

6. Cultures of the short solid D₂ types have proved nonvirulent with such regularity that whenever we are sure that the type is true we do not hesitate to report negatively on the culture and release quarantine. Although this method has been in practice for several years and concerned the discharge of hundreds of cases, no return cases can be attributed to the presence of these bacilli in the throats or noses of their hosts.

The majority of the cultures tested by us were from patients who had been in the hospital for fifteen to twenty-two days, and after the disappearance of clinical evidences of the disease. A few cultures were tested in the first week of the disease, especially when the clinical evidences of diphtheria were slight or atypical.

The results of the virulence tests according to the day of disease are shown in Tables 7 and 8.

Table 7 is a summary of the positive results observed with granular or beaded bacilli from the throat, nose and ear; Table 8 is a similar summary of the positive results with the long, solid C₂ types of bacilli. The numbers of cultures tested of barred bacilli were too few to prepare a table, and the short solid B₂ types of bacilli were uniformly without virulence in these tests.

TABLE 7.—A SUMMARY OF POSITIVE VIRULENCE TESTS WITH GRANULAR DIPHTHERIA BACILLI AT VARYING INTERVALS AFTER INFECTION

Week of Disease	Percentage of Positive Virulence Tests		
	Throat	Nose	Ear
1	100	70	50
2	70	100	68.7
3	67.5	80.6	80.0
4	73.9	75.0	60.0
5	83.3	75.0	66.6
Over 5	91.0	86.6	100.0

TABLE 8.—A SUMMARY OF POSITIVE VIRULENCE TESTS WITH SOLID DIPHTHERIA BACILLI AT VARYING INTERVALS AFTER INFECTION

Week of Disease	Percentage of Positive Virulence Tests		
	Throat	Nose	Ear
1	None tested	40.0	50.0
2	68.2	14.3	14.3
3	41.7	41.3	37.5
4	51.1	42.3	30.0
5	57.1	23.5	None tested
Over 5	47.7	40.0	0

These tables are not composed of the results observed of testing the cultures of a group of patients at regular intervals, but were compiled from the 1,054 tests.

As shown in these tables, a percentage of cultures retain their virulence for indefinite periods after the disappearance of clinical evidences of infection. In other words, virulent bacilli are likely to retain their virulence for prolonged periods when tested at intervals, so that negative virulence tests are not to be expected on the basis of duration of

disease alone; in a given case the tests are likely to yield persistently positive results as long as that particular culture of diphtheria bacilli is secured in culture. As previously stated, however, in our experience a small percentage of cultures presenting the same morphology were observed to lose virulence as tested at varying intervals; it is probable, however, that the majority of negative virulence tests following previous positive results are due to the fact that the virulent bacilli have gradually disappeared or their colonies were overlooked in the cultures.

PRACTICAL VALUE OF VIRULENCE TESTS

In the handling of diphtheria, second only in importance to the prompt, vigorous and specific treatment of the disease itself is the determination of the time when the individual ceases to possess the power of infecting others. This applies to "carriers" as well as to convalescents from clinical diphtheria.

As already stated, virulence tests may serve a useful function in differentiating between virulent and nonvirulent diphtheria bacilli when the micro-organisms persist over long periods of time on the mucous membranes or in persons who carry these bacilli, either after or without contact with a clinical case of diphtheria.

For the proper management of diphtheria according to bacteriologic examinations, an effort must be made to differentiate between the harmful and harmless bacilli. For instance, a "carrier" may be quarantined forever if guided by the fact that the presence of a diphtheria-like bacillus means diphtheria. The medical attendant must be convinced of the value of bacteriologic examinations and of the earnest efforts of the bacteriologist to work with him both in the interests of his patient and for the public welfare. The practitioner must be taught not to be afraid to report all of his cases and to culture faithfully. If, however, bacteriologic examinations serve to give unnecessary embarrassment to the practitioner by quarantining "carrier" cases, or by maintaining a quarantine unnecessarily long after convalescence as a result of conscientious efforts on the part of the latter to do his duty in taking cultures, he is not likely to give his best cooperation, and without this no real good is possible.

In the Philadelphia Hospital for Contagious Diseases in all instances in which the virulence test is negative the patient is considered noninfectious and fit for release from quarantine, regardless of what the cultures may show. These cases have been followed closely and the number of "return" cases has become practically negligible. On the other hand, we have on several occasions observed that convalescent children harboring virulent bacilli as determined by animal inoculation test, but subsequently released from quarantine on the basis of two or

three negative cultures, have been responsible for the infection of others.

The results have shown quite definitely that the virulence test is the safest and nearest perfect method that has been devised, and regardless of all things else, in the face of negative pig test, the patient is discharged; in the face of a positive test he is detained.

If the physician will take cultures carefully, conscientiously and freely, especially several cultures, before excluding the diagnosis of diphtheria in a given case, and if three consecutive negative cultures are required instead of two before quarantine is lifted, combined with the efforts of the bacteriologist to differentiate between virulent and nonvirulent bacilli, with the judicious use of the animal inoculation test in suitable cases, we believe that the bacteriologic diagnosis and management of diphtheria will be efficient and satisfactory to all.

CONCLUSIONS

1. Animal inoculation tests have been found of great value in determining the virulence of diphtheria bacilli.

2. Virulence tests are the only practical and safe means of determining the possible harmfulness of diphtheria bacilli.

3. Virulence tests have been found useful in the management of diphtheria bacillus "carriers," especially from the standpoint of duration of quarantine. This applies to healthy "carriers" discovered as the result of cultures, and to convalescents and persons showing atypical or slight clinical evidences of infection of the throat, nose, eye, wounds, etc., with cultures showing the presence of diphtheria bacilli.

4. Virulence tests in order to be practical and reliable must be sufficiently delicate to detect low degrees of virulence and this constitutes the first and important essential; it is desirable to conduct the test as economically and as speedily as consistent with specificity and delicacy.

5. Subcutaneous injection of 250 to 300 gm. guinea-pigs with cultures was found to yield better results than intracutaneous and intraperitoneal injection. The subcutaneous injection of 4 c.c. of a good twenty-four-hour culture of diphtheria bacilli on a tube of Loeffler's medium washed off with 10 c.c. of normal salt solution, was found as delicate and specific in its results as any method, besides being a test requiring a short space of time for its conduct.

A second method yielding excellent results, but requiring more time, consists in cultivating the bacilli in serum dextrose broth for seventy-two hours and injecting 250 to 300 gm. pigs subcutaneously with 1.3 to 1.5 c.c. of unfiltered culture.

6. Local edema and even slight evidences of toxemia of the test animal with absence of those signs in the antitoxin control, are regarded

as indicating virulence even though the animal does not succumb in the four-day period of observation.

7. Granular types of diphtheria bacilli were found virulent in about 70 per cent. of cultures from the throat, nose and ear; barred bacilli were found of equal virulence with the granular types. Long solid bacilli were found virulent in about 42 per cent. of cultures; cultures of short solid bacilli were found uniformly to possess no virulence.

8. Virulence tests were found of most value in determining the potential harmfulness of the solid varieties of diphtheria bacilli because these types are especially likely to be found in carriers.

METHODS OF USING DIPHTHERIA TOXIN IN THE SCHICK TEST AND OF CONTROLLING THE REACTION

RESULTS OBTAINED WITH THE TEST IN 2,700 CHILDREN*

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The practical value that the Schick reaction¹ has acquired in the diagnosis of susceptibility or immunity to diphtheria makes it desirable to say a few words about the toxin used in the test, the overneutralized or the heated toxin used in the control test, about the technic of the test, and finally about the interpretation of the reactions.

The diphtheria toxin for use in the Schick test consists of a broth culture of the diphtheria bacillus, which has been grown in the thermostat at 37 C. for six days. To kill the living organisms 10 parts of a 5 per cent. solution of phenol (carbolic acid) (0.5 per cent.) are then added, and the bacteria allowed to sediment by keeping the broth culture in the ice box during the following two or three days. The supernatant culture fluid is now passed through a Berkefeld filter, and the clear filtrate of toxin standardized. This is only a preliminary standardization. Since a considerable part of the toxin is converted into toxoids during the succeeding twelve to eighteen months, we have to use, for purposes of the Schick test, a toxin that has been ripened for at least a year, and then carefully standardized by determining the M.L.D. of the toxin for a 250-gram guinea-pig. One fiftieth of the M.L.D. in 0.2 c.c. of sterile physiologic salt solution is injected intracutaneously on the flexor surface of the forearm or arm.

The undiluted diphtheria toxin can be obtained either in bulk (vials of 2 c.c.) or in the single outfits devised by me.

The bulk toxin will keep its strength very well if a ripened toxin is used. A *primary dilution* of the toxin is first made by adding 100 M.L.D. to a sufficient amount of sterile physiologic salt solution to make

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1. Schick, B.: Spezifische Therapie der Diphtherie, Centralbl. f. Bakteriol., 1. Abt., 1913, lvii, Ref., Beiheft 16-35. Schick, B.: Die Diphtherietoxin-Hautreaktion des Menschen als Vorprobe der prophylaktischen Diphtherieheilseruminjection, München. med Wchnschr., 1913, lx, 2608.

10 c.c. For instance, if the M.L.D. of the toxin is 0.007 c.c., then 0.7 c.c. of the undiluted toxin is added to 9.3 c.c. of salt solution. Each cubic centimeter of the primary dilution will represent 10 M.L.D. This primary dilution will keep in the ice box for about two weeks. For the Schick test a fresh *final dilution* is made daily, or whenever required, by drawing up with the record syringe 1.0 c.c. of the primary dilution and adding it to 99 c.c. of sterile salt solution. Several bottles of saline (99 c.c.) may be conveniently kept on hand. The final dilution represents in 1.0 c.c. 1/10 M.L.D., and in 0.2 c.c. 1/50 M.L.D., the amount injected intracutaneously in the test. This method of diluting the toxin is convenient for use in institutions, where a large number of children are to be tested at one time, or in places where the daily carrying out of the test requires that a fresh dilution of toxin be frequently prepared. If the undiluted toxin and the primary dilution are kept very cold (45 F. or less), there will be no danger of deterioration, and the results with the test will be reliable.

In view of the necessity of the general practitioner's having a more convenient way of obtaining the undiluted toxin and of diluting it with the proper amount of sterile saline, an outfit has been devised which can be obtained by physicians in New York City from the Bureau of Laboratories of the Department of Health. These outfits are also supplied by several commercial laboratories. The outfit has been described in a previous communication.² Owing to a slight modification the essential parts of the outfit will be given again.

2. Zingher, Abraham: A Simple Outfit for the Distribution of Toxin for the Schick Test, Jour. Am. Med. Assn., July 24, 1915, p. 329.

In each package there is a capillary tube, which contains a little over 1 M.L.D. of ripened, undiluted diphtheria toxin; a small rubber bulb, similar to the ones used in the vaccine outfits, and a bottle, which contains 10 c.c. of sterile physiologic salt solution. To use the outfit one end of the capillary glass tube is broken off, and the end carefully pushed through the neck of the rubber bulb, until it punctures the diaphragm within, and enters the cavity of the bulb; the other end of the tube is then broken off. The bulb is now held between thumb and middle finger, the index finger placed over the opening in the larger end of the bulb and the toxin expelled into the saline. The capillary tube is rinsed out by drawing up saline several times, the bottle is corked and the diluted toxin shaken. Each cubic centimeter of the dilution represents 1/10 M.L.D., and every 0.2 c.c. 1/50 M.L.D., the amount used in the test. The capillary tubes with the toxin may also be obtained in quantities of 6 and 12. By refilling the 10 c.c. bottle with sterile salt solution or with cool boiled water, a fresh dilution can, whenever required, be readily prepared.

The undiluted toxin in the capillaries will deteriorate very little, if care is taken to keep the outfits in a very cold place. The diluted toxin should not be used after twelve to twenty-four hours. Each capillary tube contains a small excess of toxin (1¼ M.L.D.) to allow for any possible slight deterioration.

It was with the hope of popularizing a test, which has given us³ and others⁴ such reliable results, especially in children up to the age of 15 years, when pseudoreactions are relatively rare, that this outfit has been devised and made available for the general practitioner. No stronger proof of the reliability of the reaction need be offered, than the fact that of 1,000 patients sick with scarlet fever at the Willard Parker Hospital, who had given a negative test on admission, not one developed clinical diphtheria, although no antitoxin had been injected, and about 15 to 20 per cent. of the children showed, during their stay in the institution, virulent diphtheria bacilli in throat cultures.

The three prerequisites for the test are: (a) a reliable toxin, (b) a proper technic, and (c) a correct interpretation of the reaction. Care in getting and keeping the toxin will answer the first. A good syringe (preferably a 1 c.c.) and a fine, sharp, but short-beveled platinum-iridium needle are needed for the second. The ability to carry out the test properly is easily acquired. One point that may serve in guiding one in the injection of the diluted toxin might be emphasized. If the needle has been inserted into the proper layer of the epidermis, then the oval opening of the needle will be visible through the superficial layers of cells. A definite wheal-like elevation, with the distinct markings of the openings of sweat glands, shows that the injection has been made properly, and that the fluid is confined to small area of the epidermis. Here it will exert its irritant action, if the individual tested is not immune to diphtheria.

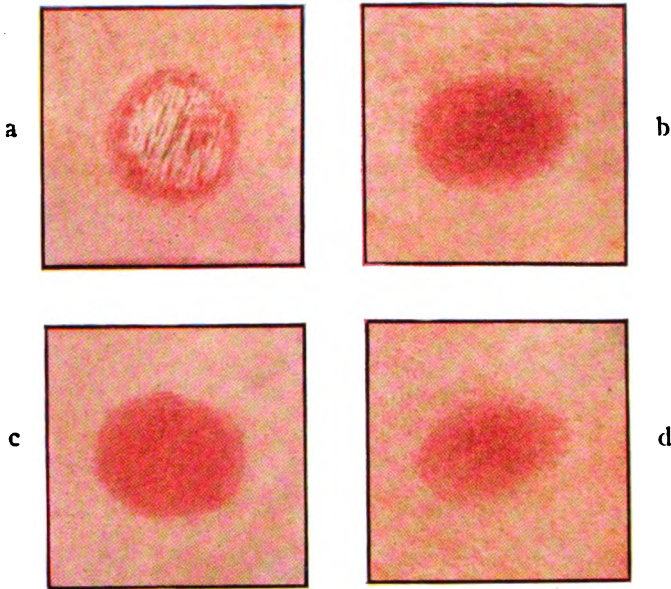
3. Park, W. H., Zingher, Abraham, and Serota, Harry M.: The Schick Reaction and Its Practical Applications, *Arch. Pediat.*, 1914, xxxi, 481. Park, W. H., and Zingher, Abraham; Practical Applications Obtained from the Schick Reaction, *Proc. New York Path. Soc.*, October, 1914. Zingher, A.: The Schick Reaction and Its Practical Applications, *Med. Rec.*, 1915, lxxxvii, 752. Overton, F., Zingher, A., and Turrell, G. H.: The Use of the Schick Test in the Suppression of a Diphtheria Outbreak, *Month. Bull. New York State Dept. Health*, 1914, xxx, 279.

4. Weaver, G. H., and Maher, L. K.: The Diagnostic Value of the Intracutaneous Injection of Diphtheria Toxin (Schick Reaction), *Jour. Infect. Dis.*, 1915, xvi, 292. Kolmer, J. A., and Moshage, E. L.: The Schick Toxin Reaction for Immunity in Diphtheria, *AMER. JOUR. DIS. CHILD.*, 1915, ix, 189. Bundesen, H. N.; Schick Reaction, with a Report of 800 Tests, *Jour. Amer. Med. Assn.*, 1915, lxiv, 1203. Moody, E. E.: The Intradermic Diphtheria Toxin Test, *Jour. Am. Med. Assn.*, 1915, lxiv, 1206. Birnberg, T. L.: The Schick Reaction and Its Practical Application, *St. Paul Med. Jour.*, 1915, xvii, 204. Graef, C., and Ginsberg, G.: Some Observations of the Schick Test, *Jour. Am. Med. Assn.*, 1915, lxiv, 1205. Linenthal, H., and Rubine, S. H.: Use of Schick Test in Children's Institutions, *Boston Med. and Surg. Jour.*, Sept. 16, 1915. Von Gröer, F., and Kassowitz, K.: Studien über die normale Diphtherieimmunität des Menschen. I. Ueber die Natur des normalen menschlichen Diphtherieschutzkörpers, *Ztschr. f. Immunitätsforsch. u. exper. Therapie*, 1914, Orig. xxii, 404; Studien über die normale Diphtherieimmunität des Menschen. II. Ueber das Verhalten des normalen Diphtherieantitoxins bei Mutter und Neugeborenen, *Ztschr. f. Immunitätsforsch., u. exper. Therap.*, 1914, Orig. xxiii, 108.

For the interpretation of the test, it is important to remember that the *positive* reaction (Plate I) represents the action of an irritant toxin on unprotected cells. A trace of redness appears slowly at the site of injection in from twelve to twenty-four hours, and usually a distinct reaction in the course of twenty-four to forty-eight hours. The reaction reaches its height on the third or fourth day and gradually disappears, leaving a definitely circumscribed scaling area of brownish pigmentation, which persists for three to six weeks. At its height the positive reaction consists of a circumscribed area of redness and slight infiltration which measures from 1 to 2.5 cm. in diameter. The degree of redness and infiltration varies to a great extent with the intensity of the reaction. In the *negative* reaction, the skin remains normal. In the *pseudoreaction* (Plate II, a, b) there is an anaphylactic response of the tissues cells to the protein substance of the autolyzed diphtheria bacilli, which is present in the toxic broth used for the test. Like other anaphylactic skin phenomena, the reaction is of an urticarial nature, appears early, within six to eighteen hours, reaches its height in thirty-six to forty-eight hours, and disappears on the third or fourth day, leaving no pigmentation or only a poorly-defined, small, brownish spot. At its height the pseudoreaction shows varying degrees of infiltration, and appears as a small central area of dusky redness, with a secondary areola, which gradually shades off into the surrounding skin. A control test may be made by injecting into the other forearm in the same dilution, diphtheria toxin which has been either heated to 75 C. for five minutes to destroy the soluble toxin, or has been overneutralized by the addition of antitoxin. This mixture is prepared by adding two units of antitoxin to each L + dose of toxin. If the first test gave a positive reaction, then the control test will be negative. If the original test was a pseudoreaction, then the control will show a similar area of redness and infiltration, and both reactions will run the same clinical course, namely, disappear in three to four days and leave little if any pigmentation behind. Since the free toxin in the solution has been either destroyed by heat or neutralized with antitoxin, the only active substances that remain are the protein of the autolyzed diphtheria bacilli and the constituents of the nutrient broth. Sterile broth in the same dilution will not as a rule give the pseudoreactions; in a lesser dilution it will show in some a faint reaction. The trace of added antitoxin (one part to a million) will not by itself show any reaction. We must, therefore, conclude that it is the protein of the autolyzed diphtheria bacilli, which is the active agent. Similar and even more intensive pseudoreactions may be obtained with a dilution of an autolysate of diphtheria bacilli, which contains no trace of soluble toxin. Overneutralized diphtheria toxin or heated toxin, for use in the control tests, can be obtained in capillaries similar to those for the Schick test.

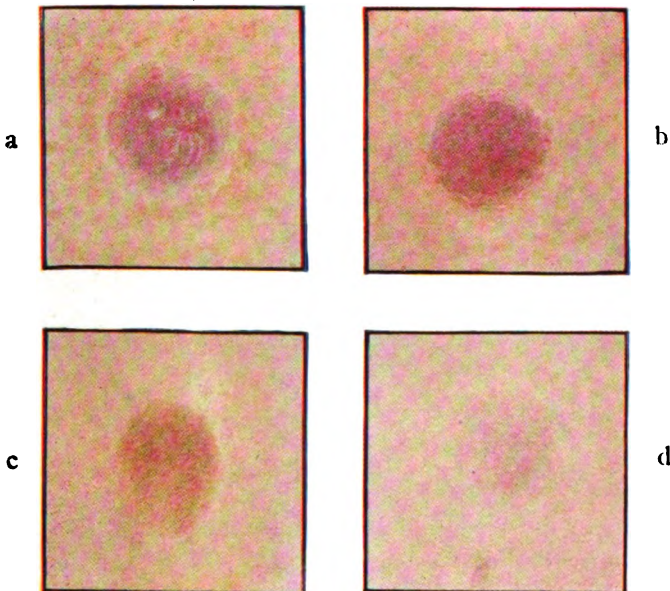
PLATE I

A



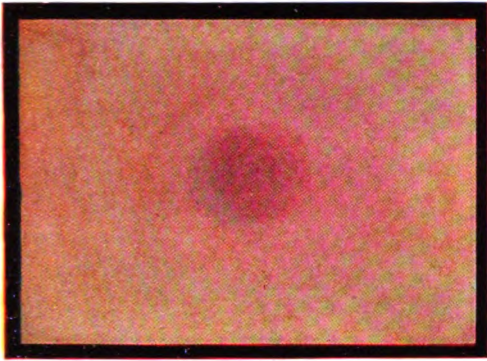
A—Shows four typical positive Schick reactions of varying degrees of intensity forty-eight hours after test; (a) is a strongly positive reaction, with vesiculation of the surface layers of the epithelium, which is seen occasionally in individuals who have practically no antitoxin; (b) and (c) are positive reactions; (d) a moderately positive reaction.

B

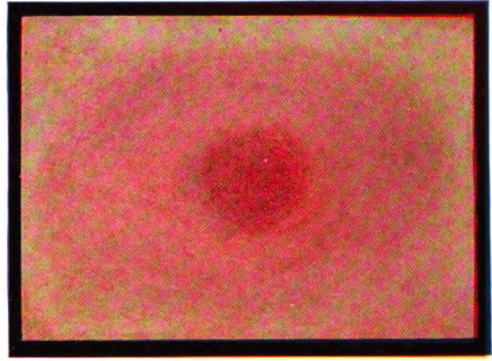


B—Shows a fading positive Schick reaction one to four weeks after test in various stages of scaling and pigmentation; (a) shows redness, scaling and beginning pigmentation after one week; (b) and (c) pigmentation after two and three weeks; (d) faint pigmentation after four weeks.

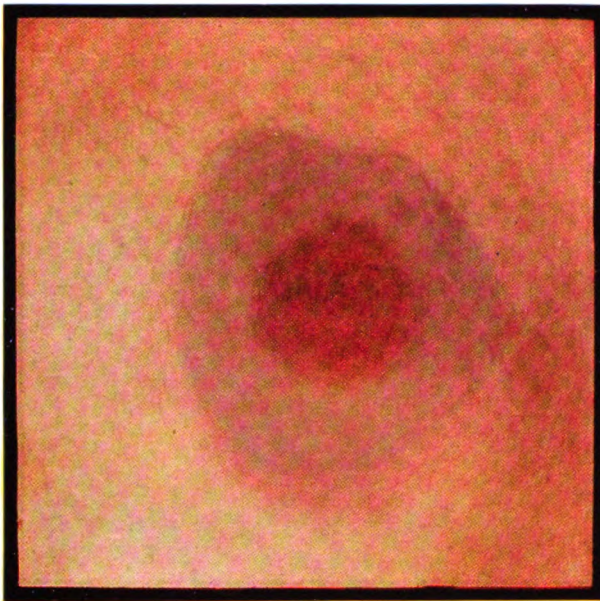
PLATE II



a



b



c

Shows two pseudoreactions forty-eight hours after test, and a combined reaction; (a) mild; (b) marked; (c) a combined positive and pseudoreaction.

Occasionally one sees a *combined reaction* (Plate II, c) which represents both a positive and a pseudoreaction. The central area of redness is larger and better defined; the amount of infiltration is also more marked. To interpret such a reaction we should obtain the evidence of a true reaction, a definite area of scaling brownish pigmentation after the pseudo element has disappeared in the test. In addition, we should obtain a similar, though weaker reaction in the control test made with heated or overneutralized toxin. The control will, of course, represent only the pseudoreaction. These pseudoreactions are rarely seen in the young, but quite frequently in the adult. Unless one is able carefully to differentiate them from the positive reactions it will be safer in practice to consider all reactions as positive, and treat them as such on exposure to diphtheria.

For purposes of recording the tests we may designate the positive reaction by the following signs, which represent varying degrees of intensity. This is especially important in the active immunization with mixtures of diphtheria toxin and antitoxin when we wish to know the degree of the original or control test before the immunizing injections, and of tests made at intervals after the injections.

- + + strongly positive. Marked redness and considerable local infiltration, occasionally superficial vesiculation.
- + positive. Redness and little or no local infiltration.
- ± moderately positive. Varying degrees of redness and no local infiltration.
- ± faintly positive. Slight redness and no local infiltration.
- negative. No redness and no local infiltration.

Several groups of healthy children were tested with the Schick reaction and the results shown in the accompanying table obtained:

SUMMARY OF SCHICK TESTS FROM THREE LARGE ORPHAN ASYLUMS
(NORMAL CHILDREN)

Age Years	Total	— Schick	+ Schick	Per Cent. + Schick
2- 4	62	42	20	32.2
4- 6	318	236	82	25.7
6- 8	444	347	97	21.8
8-10	597	462	135	22.6
10-12	584	459	125	21.4
12-14	506	416	90	17.7
14-16	189	158	31	16.4
	<hr/> 2,700	<hr/> 2,120	<hr/> 580	<hr/> 21.4

It is rather important to note in our table of normal children, that not more than 17 to 32 per cent. of children between the ages of 2 and 14 years gave a positive reaction. This is a significant factor in the active immunization against diphtheria with mixtures of toxin-

antitoxin, since the relatively small number of individuals that need to be protected makes the work, from the ease with which it could be accomplished, of distinct practical value. In some 1,200 children suffering with scarlet fever we had found a larger proportion (65 per cent.) of positive reactions between the ages of 2 and 6 years. This is possibly due to the fact that the higher temperature of scarlet fever with the associated increased metabolism of the body causes a breaking down of the trace of natural antitoxin, which is just sufficient to give a negative reaction in some of the healthy children; possibly, also, those who are susceptible to scarlet fever are more apt to be susceptible to diphtheria, that is, give a positive Schick reaction.

Combined reactions were noted among the reactors in this group in about 10 per cent. of the older children, especially among the females; a smaller proportion of the children showed pseudoreactions.

The testing of large numbers of children can be easily accomplished, if the children are standing in line and their forearms have been exposed and cleaned with alcohol. With a properly working syringe and needle, each operator can make as many as 200 to 250 tests an hour, the needle being rapidly cleaned between the injections with a cotton sponge saturated with alcohol. The children should be seen at the end of twenty-four hours to determine the presence of the pseudo and combined reactions; they should be seen again in forty-eight and seventy-two hours. Careful notes should be kept of the character of the reactions, and the pseudoreactions should be controlled, for the sake of accuracy and experience, with the heated or overneutralized toxin. Individuals who give a pseudo or a combined reaction are much more susceptible to the local action of antitoxic serum, or of immunizing injections of toxin-antitoxin serum.

The testing of children on a large scale in schools and institutions can be thus readily accomplished and a permanent record kept of the reactions. From the results which we have obtained in the testing of older children and adults we feel fairly certain that the majority of children who have reached school age and show a negative reaction, are protected for years and probably for life.

The data that we thus obtain will represent valuable facts both for the individual and for the community. For the individual the assurance of an immunity to diphtheria will save many an hour of worry over repeated attacks of catarrhal laryngitis, or a suspicious tonsillar exudate in which possibly a positive bacteriologic examination has been made. For the community we may, with an increasing knowledge of the number of permanent immunes, and the careful study of the transition periods of the susceptible individuals to a stage of immunity, as well

as the carrying out of an active immunization⁵ of the susceptible ones, be finally able to control a disease which continues to be one of the big issues of preventive medicine. The failure so far has been made especially evident by our attempts to deal with the problem of the bacillus carrier. It will probably not be by the elimination of the bacillus carriers, but rather by the active and possibly permanent immunization of the susceptible individuals in a community that we will prevent fresh cases of infection and, to some extent at least, the development of new foci for the dissemination of virulent diphtheria bacilli.

CONCLUSIONS

1. The great practical value connected with the Schick test makes it desirable that the results obtained with it should be reliable.

2. The accuracy of the results will depend not only on the toxin, but also on the care with which the test is made, and on the interpretation of the reaction.

3. The undiluted toxin is available in bulk or in capillary tubes. It should be well ripened and always kept very cold and in a dark place.

4. The positive reaction should be considered as indicating a lack of immunity, unless the pseudoreaction can be eliminated by a control test. The negative reaction is a definite sign of immunity.

5. It is important to remember that, in using diphtheria toxin in the Schick test, we are dealing with an accurate quantitative reaction, and handling carefully measured amounts of an active agent, that has a tendency to deteriorate, even in bulk, if it is not properly protected from light and exposure, and kept in a very cold place.

6. The results with the test obtained in 2,700 normal children, show that from 17 to 32 per cent. between the ages of 2 and 16 years give a positive reaction and are probably susceptible to diphtheria.

5. Von Behring: Ueber ein neues Diphtherieschutzmittel, *Deutsch. med. Wchnschr.*, 1913, xxxix, No. 19. Park, W. H., Zingher, Abraham, and Serota, Harry M.: Active Immunization in Diphtheria and Treatment by Toxin-Antitoxin, *Jour. Am. Med. Assn.*, Sept. 5, 1914, p. 859. Park, W. H., and Zingher, Abraham: Active Immunization with Diphtheria Toxin-Antitoxin, and with Toxin-Antitoxin Combined with Diphtheria Bacilli, *Jour. Am. Med. Assn.*, Dec. 18, 1915.

D'ESPINE'S SIGN IN CHILDHOOD *

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This study was undertaken because of the difference of opinion which prevails as to what constitutes D'Espine's sign, and because of my impressions that D'Espine's sign is much less often present in the children of the well-to-do than in those of the hospital class, and that, when present in children of this class, it is in a considerable proportion of the cases not a manifestation of tuberculous infection. Six hundred and sixty-six patients, seen in my consultation and office practice during the last three years, form the basis of this study. These children were consecutive, except when for some reason they were unable, or unwilling, to talk, or when, through some oversight, a test was either not made or no record kept of it. The sign was tried for simply as part of the routine physical examination, and at the time the tests were made I had no intention of using the results for any purpose. The conclusions derived from these results, therefore, should be entirely unbiased.

Professor Adolphe D'Espine of Geneva in an article on "The Early Diagnosis of Tuberculosis of the Bronchial Glands in Children,"¹ said that he had called attention briefly to this method of diagnosis in 1889, in the fourth edition of the "Manual of Picot and D'Espine," and that Professor Brouardel, in a communication made for him at the session of the Academy of November 8, 1904, said: "The first signs of bronchial adenopathy are furnished exclusively by the *auscultation of the voice*, and are found almost always in the immediate neighborhood of the vertebral column between the seventh cervical vertebra and the first dorsal vertebra, sometimes in the fossa "sus-épineuse," sometimes in the interscapular space. They consist in a quality (timbre) added to the voice, which may be called *whispering (chuchotement)* in the first stage and *bronchophony* in a more advanced stage." He then goes on to say that "it is most important to distinguish the exaggerated normal voice sound from the bronchial voice sound. He says that "the tracheal sound is heard normally through the seventh cervical

* Submitted for publication Feb. 7, 1916.

* Read at the meeting of the New England Pediatric Society, Feb. 4, 1916.

1. D'Espine: Bull. de l'Acad. de méd., Paris, 1907, Series 3, lvii, 167; British Med. Jour., 1910, ii, 1136.

spine, where it ceases abruptly. In bronchial adenopathy the bronchial sound extends downward into the space between the seventh cervical and the fourth or fifth dorsal spines. This space corresponds to the last portion of the trachea and the bifurcation of the bronchi, which is at the level of the third dorsal vertebra." He recommends the use of 333, in French, for making the test, and says, "if auscultation of the loud voice or cry gives no result, the child should be made to speak in a low voice." A sound is then heard which he designates as "whispering (*chuchotement*). "This sound has the same value as bronchophony."

TABLE 1.—SHOWING PRESENCE OR ABSENCE OF D'ESPINE'S SIGN AT VARIOUS AGES

Age, Years	Present	Absent	Total	Per Cent.
1-2	1	63	64	1.6
2-3	1	79	80	1.3
3-4	1	59	60	1.7
4-5	1	83	84	1.2
5-6	5	91	96	5.2
6-7	5	68	73	6.8
7-8	9	70	79	11.4
8-9	9	42	51	17.6
9-10	3	20	23	13.0
10-11	4	33	37	10.8
11-12	1	18	19	5.3
	40	626	666	6.0

In a later communication in the *British Medical Journal* of 1910, he says that "the sign is most obvious when the child is made to speak or count in a low voice. The voice is then accompanied by an added whispering sound localized to one or two vertebrae, or possibly extending to the fourth or fifth. A bronchial quality to the respiration at the same place has the same diagnostic value as the whispered sound. It is necessary to be content with this, if the child is too young to speak, but the bronchial breathing is a sign of enlargement already more considerable and more extensive. It is the same with vertebral percussion."

Having read only D'Espine's articles when I began to test for the presence of this sign, I naturally took for the line dividing the normal from the abnormal, the line between the seventh cervical and first

TABLE 2.—DATA CONCERNING D'ESPINE'S SIGN

Age, Yrs.	Location	Remarks
1½	5 D	Tuberculin test positive.
2¼	?	Typhoid fever; father perhaps tuberculous.
3½	?	Asthma.
4	3 D	Adenoids.
5	4 D	Frequent "colds"; sign gone 2½ years later.
5½	4 D	Asthma.
5¾	?	Tuberculosis of knee.
5¾	?	Just over bronchopneumonia.
5¾	4 D	Chronic bronchitis; influenza bacilli found.
6	4 D	"Below par"; normal otherwise.
6	5 D	Acute bronchitis.
6½	5 D	Bronchitis; gone seven months and three years later.
6½	4 D	Just over pertussis; had tuberculous glands in neck two years before.
6¾	?	Delicate child; known exposure to tuberculosis.
7	5 D	Acute endocarditis.
7	?	Epilepsy.
7	3 D	Recurrent bronchitis.
7¼	4 D	Chronic valvular disease; sign absent five months before.
7½	?	Just over "cold"; absent two years before.
7½	4 D	Chronic bronchitis; no tubercle bacilli in sputum; tuberculin test neg.
7½	?	Bronchopneumonia.
7½	?	"Cold" for four weeks.
7¾	?	Feeble-minded.
8	3 D	Delicate child; recurrent bronchitis.
8	3 D	Bronchitis and asthma.
8	4 D	Acute bronchitis
8	3 D	Habit spasms.
8¼	?	Cervical adenitis, probably tuberculous.
8¼	?	Delicate child.
8¼	?	Known exposure to tuberculous milk.
8½	4 D	Bronchitis and asthma; tuberculin test positive.
8½	?	Masturbation; sign present two years later, but child very well.
9	?	Acute yellow atrophy of liver.
9	4 D	No disease.
9½	?	Adenoids and large tonsils.
10	1 D	Tuberculosis of lungs and cervical glands.
10½	2 D	Chorea.
10½	?	Hysteria; tuberculin test positive.
10¾	3 D	Delicate child; functional heart disease.
11	4 D	Delicate child.

dorsal spines. Both the whispered voice and the spoken voice were used in making the tests. In some cases one was more satisfactory, in others, the other. In rare instances, in the younger children, the cry was used. No conclusions were drawn from the character of the respiration alone. In 626 of the 666 children, or 94 per cent., the change in the voice sound occurred between the seventh cervical and the first dorsal spines. These figures seem sufficient to prove that in childhood D'Espine's original contention as to the location of the normal change in sound is correct. They also seem to show that those who state that the change in sound normally occurs at the second dorsal spine or, as some say, at the fourth dorsal spine, are wrong in their statements.

The fact that D'Espine's sign was present in but forty of 666 children, or only 6 per cent., shows that D'Espine's sign is uncommon in the children of the wealthy and well-to-do classes of our community. The accompanying table (Table 1) shows that D'Espine's sign is very seldom present in these children before 5 years, that it is most common between 8 and 9 years, and that its frequency diminishes from that time on.

Table 2 shows the ages at which the sign was found, the location of the change in sound when it was specified in the notes, and such other data as seem of importance.

It is, of course, impossible to analyze such a table accurately. It would seem, however, that in eighteen, or nearly 50 per cent., of the children the enlargement was probably not tuberculous. In nine it probably was tuberculous, and in thirteen there is no data pointing either one way or the other. These figures show what is now generally accepted, namely, that D'Espine was wrong in his conception that his sign was always a manifestation of tuberculosis of the bronchial glands. The presence of this sign means merely that there is some tissue between the trachea and bronchi and the vertebral column which transmits the bronchial sound unchanged, whereas under normal conditions it is modified during its transmission. This tissue is ordinarily made up of the enlarged tracheobronchial lymph nodes. The enlargement of these nodes may or may not be due to tuberculosis. These figures also seem to show that among the well-to-do-classes enlargement of the tracheobronchial lymph nodes is almost, if not quite, as often non-tuberculous as tuberculous. Too much importance cannot be attached to them, however, because positive proof as to the nature of an enlargement of these nodes can be furnished only by necropsy. It is especially noticeable how frequently they are enlarged in asthma with chronic bronchitis.

CONCLUSIONS

The following conclusions seem warranted from the study of these cases:

D'Espine was correct in his original contention that the normal change in the voice occurs between the seventh cervical and the first dorsal spines.

D'Espine's sign is present, therefore, when the bronchial voice, or whisper, is heard below the seventh cervical spine.

D'Espine's sign is uncommon in children of the well-to-do classes. When it is present in them, it is probably not a manifestation of tuberculosis in more than 50 per cent.

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ACROCEPHALOSYNDACTYLISM—A TERATOLOGICAL TYPE *

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Acrocephalosyndactylie (Apert), acrosphenodactylie (Maygrier) or acrocephalosyndactylism, was first described by Troquart¹ in 1886. Since the first description there have been ten other cases noted, namely, those of Beno² in 1886, Galippe and Magnan³ in 1892. Wheaton,⁴ two cases, in 1894, Dubrisay⁵ in 1898, Maygrier⁶ in 1898, Fournier⁷ in 1898, Camus⁸ in 1905, Davis⁹ in 1915, and Bertolotti and Boidi-Trotti¹⁰ in 1915. Two other cases of symmetrical syndactylism with pathological changes in the bones of the head have been described but the descriptions are not of sufficient exactness to allow a diagnosis to be made. These cases are those of Parham¹¹ and Haultain.¹²

Apert,¹³ in 1906, described the condition at length, and later Sterling,¹⁴ in 1914, in a review of the trophic diseases, deformities and delayed development of the osseous system, collected and reported cases to date and discussed the principal characteristics, which are as follows: The cranium shows a marked lengthening in the external distance from the nasion to the inion. The anteroposterior diameter is greatly shortened. The superciliary ridges are highly arched and flattened and the brow bulging. The orbits are also flattened anteroposteriorly, which, together with the deformity of the superciliary ridges,

* Submitted for publication Jan. 29, 1916.

* From The Babies' Dispensary and Hospital and the Pediatric Department of Western Reserve Medical School.

1. Troquart: Bull. et. mém. Soc. de chir. de Bordeaux, 1886, p. 69.

2. Beno: Thèse de Nancy, 1886, Observation xxix.

3. Galippe and Magnan: Compt. rend. Soc. de biol., 1892, Series 9, iv, Part 2, p. 277.

4. Wheaton: Tr. Path. Soc. London, 1894, xlv, 238.

5. Dubrisay: Bull. Soc. d'obst. de Paris, 1898, i, 81.

6. Maygrier: Bull. Soc. d'obst. de Paris, 1898, p. 28.

7. Fournier, E.: Thèse de Paris, 1898, Observation cccxxvii.

8. Camus: Bull. Soc. de biol., 1905, p. 1555.

9. Davis, B. F.: Acrocephalosyndactylism, AM. JOUR. DIS. CHILD., ix, 446; Jour. Nerv. and Ment. Dis., 1915, xlii, 567.

10. Bertolotti and Boidi-Trotti: Riforma med., 1915, xxxi, 679. Boidi-Trotti: Gior. d. r. Accad. di med. di Torino, 1915, Series 4, xxi, 123.

11. Parham: New Orleans Med. and Surg. Jour., 1886, New Series, 7, xiv, 755.

12. Haultain: Edinburgh Med. Jour., 1895, xl, 658.

13. Apert: Bull. et mém. Soc. méd. d. hôp. de Paris, 1906; Series 3, xxiii, 1310.

14. Sterling: Ztschr. f. d. ges. Neurol. u. Psychiat., 1914, ix, 138.

causes a marked proptosis. There is not infrequently found a sulcus or ridge in the situation of the metopic suture. In general the head is symmetrical but in the case of Maygrier⁶ and Gallippe³ it was asymmetrical. The facial bones are profoundly altered. The zygomata are very prominent, the root of the nose depressed (saddle nose), the superior maxillae atrophic, causing the right and left alveolar borders to be pressed together, thereby forming one of the most characteristic features, namely, the very highly arched palate. In fact, this is sometimes so narrow as to give the appearance of a cleft. In those patients that have lived to a sufficient age there has been anomalous dentition. The neck, chest and abdomen show no pathologic changes. The extremities are markedly deformed by the presence of a more or less complete syndactylism. The hands are often in a position of the *main d'accoucheur*. They have been described as "spatula form." They are semi-flexed, and the palms are immobile. The thumbs are mobile and generally not involved in the syndactylism. In only one case were there separate nails. In the other cases they show more or less fusion. Various kinds of anomalous ossification have been mentioned. Probably the most constant deformity has been the fusion of the fourth and fifth metacarpals at their bases. Reduction (oligodactylism) and increase (polydactylism) in the number of the phalanges have been described, as well as the absence of the terminal phalanges (bradydactylism). The feet show anomalies similar to those in hand. Wheaton⁴ and Dubrisay⁶ report necropsies on their patients. They report the anteroposterior cranial measurements decreased, in one case the basio-occipital bone atrophic, in one premature synostosis of the tribasilar bone, and in one of Wheaton's cases the metopic suture ossified with Wormian bones. In the skull they found other supernumerary bones. The brain showed considerable compression. There were no visceral changes.

Bilateral optic neuritis has been found on ophthalmoscopic examination (Fournier⁷) and also some impairment of hearing.

Roentgenographic studies have been made in six cases—Fournier,⁷ Maygrier,⁶ Dubrisay,⁵ Davis,⁹ Bertolotti,¹⁰ and in our own case.

The condition is compatible with life. The ages of the described patients vary from new-born babies (Dubrisay⁵ and Fournier⁷) to 31 years, as in the case of Galippe and Magnan.³ The mental activity varies, but in most cases it is stated to be normal.

CASE REPORT

The following case shows all of the characteristic deformities:

History.—Patient R. Z., boy, aged 6 months, was admitted to The Babies' Dispensary and Hospital, Cleveland, with a complaint of "cold in the head."

Family History.—Mother living but has not been well since her first child was born. She has had much pain in the lower abdomen and has worn a pessary to relieve a prolapsus uteri which followed her first pregnancy. There are two other children living and well. No miscarriages. No history of tuberculosis, lues or abnormality in the development of any other member of the family. The father is in good health. The parents attribute the deformity of the patient to a gas explosion which occurred when the mother was four months pregnant.

Personal History.—Birth weight 8 pounds; full term; normal delivery by physician; resuscitation difficult. The infant was breast fed for two weeks after which he was fed irregularly on a simple milk dilution. The child was weaned because of the difficulty in breathing when on the breast. With the exception of numerous "colds in the head" the child has been perfectly well.



Fig. 1.—Enlarged veins of the scalp.

Present Illness.—For three months the child has had an increasing difficulty in breathing, accompanied by a considerable discharge of a mucous substance from the nose.

Physical Examination.—A well nourished baby of 6 months, showing numerous abnormalities in development, especially in the cranium and extremities. The turgor is normal; color of the mucous membranes good; mentality seems normal; smiles, and attention is easily distractable by sounds and light; attempts to grasp objects offered. The superficial lymph glands are of normal size.

The head presents numerous deviations from the normal, the most marked of these being the greatly increased measurement from the nasion to the inion, the pronounced bulging of the forehead, associated with a flattening of the superciliary ridges, the decreased biparietal and anteroposterior diameters, the proptosis, the depressed bridge of the nose and the marked narrowing and high arching of the hard palate. There are slight increases in the bizygomatic

and bitemporal diameters. In the anterior view the head forms a roughly triangular figure when the bizygomatic line is taken as the base and the bregma as the apex. Just above the superciliary ridges there is a marked depression in the frontal bone, giving a sulcus-like formation. This can be seen in Figure 1. The occipital region is greatly flattened. The external occipital protuberance is absent. As will be seen from the following measurements, the deformity is even greater than is apparent from the photographs:

	Diameter cm.		Circumference cm.
Fronto-occipital	11.	Fronto-occipital	38.0
Bitemporal	11.5	Occipitomental	49.0
Biparietal	10.5	Lambda and supraorbital	37.5
Frontomental	16.5	Lambda-glabella (horizontal)	37.0
Bizygomatic	12.0	Lambda-glabella (vertical)	21.0
Transorbital	8.0	Glabella to bregma (vertical)	7.75
Mento-occipital	18.0		
Bregma-inion	13.5		
Tragus-to-tragus	11.0		
Height of orbit	2.75		
Total length of child 66.5 cm.			

The anterior and posterior fontanels are open, and the coronal, sagittal and lambdoid sutures are not completely closed. The metopic suture is replaced by a ridge-like bony prominence. The roentgenogram of the head shows the presence of digital impressions in the frontoparietal region.

All the superficial veins of the scalp are greatly dilated. The temporal vein is so greatly dilated as to appear almost a sinus, and it is pulsatile.

The ears are very large and the external auditory canal is compressed anteroposteriorly, giving it a triangular shape and rendering examination of the tympanic membrane impossible. The hearing is apparently acute.

The eyes show a marked proptosis (Fig. 2). The pupils are equal in size and regular in outline. The eyelids are thickened. The outer canthus is considerably lower than the inner.

The nose is markedly depressed at the root, giving it a typical "saddle nose" appearance.

The mouth is constantly open. The tongue is somewhat larger than normal, but it appears even more so on account of its constant protrusion, caused by the short distance between the alveolar border and the postpharyngeal wall.

The hard palate is distinctly deformed. The transverse distance between the alveolar borders is considerably shortened. The palate seems to have been compressed to such a degree as to form a very acute angle. Running from before backward, this forms a narrow but deep sulcus until a short distance in front of the junction of the hard and soft palate, where it opens out laterally. The uvula is normal.

The neck, chest and abdomen are normal.

The hands show a complete syndactylism of all the fingers except the thumbs (Fig. 3-B).

Both hands are in a partially flexed condition, the angle of flexion being mainly between the metacarpals and the proximal phalanges. The thumbs are sharply flexed and adducted. The palms are of the so-called "spoon shape" (Fig. 3-B). The nails are completely fused, although some suggestion of division occurs between the second and third and between the third and fourth. The nail of the thumb is wide and heavy.

The roentgenogram of the right hand (Fig. 4) shows an absence of all the terminal phalanges, unless the break in the shadow of the second digit be interpreted as a joint. In that case it is present in this finger, but there is marked shortening of the second phalanx. The metacarpal bones are not fused. There is considerable ossification in the unciform and os magnum.

The roentgenogram of the left hand (Fig. 5) shows the same as the right, with the exception of a fusion of the bases of the fourth and fifth metacarpal bones.

The feet show a complete syndactylism which includes the great toe (Figs. 3-A and 6). They seem shorter than normal. The nails are not fused as much as in the hands. On the left foot those of the great and second toes are completely fused while the others are separate. On the right foot those of the great and first and those of the fourth and fifth toes are partly fused.



Fig. 2.—Characteristic position of tongue and mouth. Proptosis.

The roentgenogram of the left foot (Fig. 7) shows an absence of the terminal phalanges. The first phalanx is much larger than normal. Near the base of the second there is a large sesamoid bone. The first and second metatarsal bones are connected near their bases.

The roentgenogram of the right foot (Fig. 8) shows an absence of the terminal phalanges. The first phalanx is larger than normal and on its inner side there is a small notch. At the base of the second metatarsal bone on its outer surface there is a large tuberosity. The remaining metatarsal bones are rather smaller than normal and not as regular as usual.

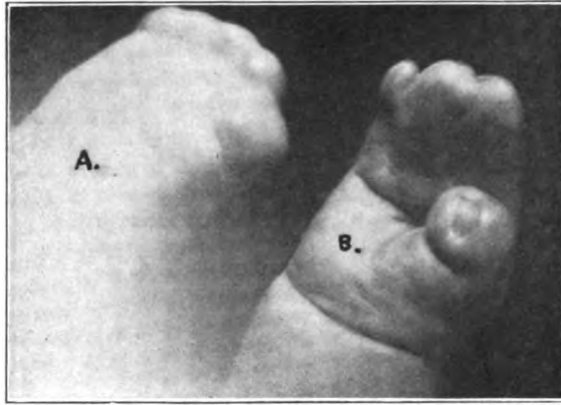


Fig. 3.—Left foot and right hand.



Fig. 4.—Roentgenogram of right hand.



Fig. 5.—Roentgenogram of left hand.



Fig. 6.—Feet, showing some fusion of nails and brachydactyly.

The occurrence of anomalies and deformities in the various forms of animal life has given rise to an immense amount of speculation as to their causation, but not until recent years has real scientific investigation been attempted to furnish a solution to these most interesting phenomena. For many years in the scientific world maternal impressions were considered as playing a fundamental part in their production, and today the laity still hold to this view. Of late years, however, numerous observers have studied the problem from a much more critical standpoint and a number of experimental attempts at the solution have been made. Stockard¹⁵ obtained quite constant results from breeding animals whose ancestors had been exposed to long periods of intoxication from inhalation of alcohol fumes. He found more congenital



Fig. 7.—Roentgenogram of left foot.

defects of the eyes in the third generation than in the second. Werber,¹⁶ by subjecting the eggs of the marine teleost fish *Fundulus heteroclitus* to butyric acid and acetone, these substances being selected because they are known to arise in various conditions of faulty metabolism in man, obtained such defects as hydrocephalus, cyclopia, and circulatory and ear vesicle defects. Hertwig¹⁷ concluded from his researches that defective development, such as spina bifida in amphibians, could be produced by subjecting fertilized ova to a 0.6 to 0.7 per cent. sodium chlorid solution. He, therefore, suggests that possibly certain monstrous formations in human beings may be due to the presence of certain poisons such as alcohol or toxins in the blood of the mother. Other recent researches by Fere and McClendon in experimental tera-

15. Stockard, C. R.: Arch. f. Entwicklungsmechn. d. Organ., 1912, xxxv, 569; THE ARCHIVES INT. MED., 1912, x, 369.

16. Werber, E. I.: Bull. Johns Hopkins Hosp., 1915, xxvi, 226.

17. Hertwig, O.: Gegenbauer's Festchrift, 1896, ii.

tology have demonstrated that various physical and chemical means can be used to cause defective or monstrous development.

Mall,¹⁸ after a study of 163 pathologic human embryos, believed that the defective development of these embryos was due to a condition which he was pleased to term faulty implantation of the ovum in the wall of the uterus. This is due not to a pathologic condition of the fertilized ovum, but to a diseased condition of the uterine wall. He concluded that from such a diseased condition of the uterine wall the adequate nutrition of the embryo would be impossible and the early death of the embryo from inanition probable. This may well explain



Fig. 8.—Roentgenogram of right foot.

the monstrous condition of those embryos which are aborted early, and even explain defective prenatal development in some of those embryos which survive.

Various other intra-uterine conditions have been advanced as the etiologic factors concerned in defective atypical developments of the ovum, such as hydramnios and oligohydramnios. Wheaton, in 1894, declared that he believed that hydramnios due to syphilis was the cause of the deformity in his cases of acrocephalosyndactylism.

The various infectious diseases have been pointed out as the etiologic factor in not a few cases of monstrous development, syphilis and tuberculosis, of course, being the diseases most commonly indicated.

18. Mall, F. P.: *Jour. Morphol.*, 1908, xix, 1-367.

One of the most attractive theories for the explanation of certain forms of atypical development is that expounded by Babes¹⁹ in 1904, and by Apert and Babes. They observed that in certain types of cranial deformity there was frequently an associated maldevelopment of the extremities and this association was of such frequency as to cause Apert and Babes²⁰ to say "A trophic correlation between the base of the brain and the development of the extremities may be presumed."

Babes²¹ says further:

A primary, deep-reaching anomaly of the face, and especially of the base of the skull, had led to an extensive modification of the four extremities. . . . Without discussing this further at present, intending to come back to it later, I believe it can be regarded as established that extensive modifications of all the extremities, which I will call *Acrometagenesen*, in consequence, in part, of pathologic changes of a certain region of the anterior base of the skull and in the upper half of the face, may occur, and these modifications are capable of throwing much light into many dark fields in the study of the origin of races and species.

That there is a trophic correlation between the base of the brain or the base of the skull and the development of the extremities is a point which would be difficult to prove by exact methods. From clinical observation, however, the fact that in numerous cases of premature fetal synostosis of the bones at the base of the skull there occur also defects in the development of the extremities, makes the theory of Babes an attractive one.

The cause or causes of the premature synostosis would still be unexplained even were this theory proved.

The regularity of the malformation, as shown by the eleven reported cases of acrocephalosyndactylism, the symmetry of the lesions and their widespread character would seem to disprove the theory of any local damage such as irregularity in the amount of amniotic fluid, for in such a case the deformities are always irregular and asymmetrical.

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19. Babes, V.: Berl. klin. Wchnschr., 1904, xli, 464.

20. Eine tropische Korrelation zwischen Gehirnbasis und der Entwicklung der Extremitäten vermuten.

21. Eine primäre tiefgreifende Anomalies des Gesichtes und besonders der Schädelbasis zu einer tiefgreifenden Umwandlung der vier Extremitäten geführt hatte.

Ohne auf diese Frage näher einzugehen, auf welche zurückzukommen ich mir vorbehalte, glaube ich als feststehend constatieren zu können, dass sich tiefgreifende Umwandlungen aller Extremitäten, welche ich "*Acrometagenesen*" nennen will, in Folge von zum Teil pathologischen Veränderungen einer bestimmten Region an der vorderen Schädelbasis und an der oberen Gesichtshälfte vollziehen können, welche Umwandlungen im Stande sind, über manche dunkle Gebiet ein der Forschung über die Entstehung des Rassen und Arten etwas mehr Licht zu verbreiten.

ON THE PRESENCE OF KETONES AND BETAHY-
DROXYBUTYRIC ACID IN THE URINE OF
NORMAL CHILDREN *

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As a part of general study of the urine of normal children under different dietetic conditions, a number of urines were studied to determine whether or not ketones and betahydroxybutyric acid were present, and if so, in what quantities. Although discussions of acidosis in childhood, and particularly of pathological conditions in which large amounts of "acetone bodies" appear in the urine are numerous, there are no figures in literature, so far as we know, in regard to the amount of these substances in the urine of "normal" or healthy children.

The method used for determining their presence was that of Shaffer, in which the acetone and the aceto-acetic acid are first distilled over, and then the betahydroxybutyric acid oxidized by potassium bichromate and distilled over as acetone. The amount of acetone is then determined by the iodimetric method of Messinger. The children from whom the twenty-four-hour specimens examined were obtained were what is usually termed "normal" with a few exceptions. In a few instances children with fully compensated chronic valvular cardiac disease were utilized, and likewise a few boys with hernias before operation. From the standpoint of their metabolism they may be regarded as normal. The diet was what we term "standard metabolic diet," whose composition will be described in a later paper. It varies for different age periods, contains fat, carbohydrate and protein in proper proportions, and is of sufficient caloric value to cover the needs of children at light work or play. The children were in bed and had been on the diet for several days before the twenty-four-hour specimen used was collected. During this time the temperature was taken frequently in order to be sure that the children were afebrile.

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In the accompanying table the results obtained from the examination of the urines of twenty-one children are tabulated. As the results were so uniform and consistent, it did not seem probable that anything further was to be gained from the study of a larger number of children. The amount of betahydroxybutyric acid is in terms of acetone.

TABLE SHOWING THE PRESENCE OF KETONES AND BETAHYDROXYBUTYRIC ACID IN THE URINES OF TWENTY-ONE NORMAL CHILDREN

Name	Sex	Condition	Age	Weight, Pounds	Acetone and Diacetic Acid	Beta-hydroxybutyric	Diet
B. Z.	M.	Normal.....	2 mos.	8½	0.011	0.022	Standard infant
E. B.	M.	Normal.....	14 mos.	25	0.087	0.012	Standard infant
R. K.	M.	Normal.....	19 mos.	26	0.080	0.017	Standard infant
W. O.	M.	Normal.....	21 mos.	22	0.015	0.020	Standard 20 to 36 mos.
A. O.	F.	Normal.....	24 mos.	28	0.010	0.022	Standard 20 to 36 mos.
J. A.	M.	Normal.....	28 mos.	24	0.040	0.041	Standard 20 to 36 mos.
P. D.	M.	Old anterior polio-myelitis	28 mos.	25	0.025	0.017	House diet
C. H.	M.	Normal.....	3 yrs.	27	0.019 0.081	0.035 0.040	Standard 3 to 6 yrs. Three weeks later
A. E.	M.	Normal.....	4 yrs.	35	0.011	0.008	Standard 3 to 6 yrs.
V. R.	F.	Healed eczema....	4 yrs.	35	0.010	0.025	Standard 3 to 6 yrs.
E. F.	M.	Normal.....	5 yrs.	40	0.017	0.029	Standard 3 to 6 yrs.
E. B.	M.	Mental deficiency backward development	5 yrs.	30	0.015	0.018	Standard 3 to 6 yrs.
L. O.	M.	Chr. valvulitis....	7 yrs.	..	0.007	0.080	Standard 6 to 10 yrs.
I. H.	F.	Chr. valvulitis....	8 yrs.	38	0.110 0.090	0.066 0.067	Creatin-free Following day
M. R.	F.	Chr. valvulitis....	9 yrs.	41	0.045	0.037	Standard 6 to 10 yrs.
W. B.	M.	Mental deficiency	9 yrs.	63	0.014 0.030	0.053 0.053	Creatin-free Following day
C. H.	M.	Hernia.....	9 yrs.	58	0.063	0.032	Standard 6 to 10 yrs.
C. F.	M.	Hernia.....	10 yrs.	..	0.012	0.020	Standard 6 to 10 yrs.
E. H.	F.	Chr. valvulitis....	10 yrs.	58	0.015	0.044	Standard 6 to 10 yrs.
L. M.	M.	Latent hereditary syphilis	11 yrs.	70	0.015 0.021	0.026 0.035	Standard 10 to 14 yrs. Three days later
T. H.	M.	Hernia.....	12 yrs.	81	0.015	0.022	Standard 10 to 14 yrs.

SUMMARY

It will be noted that small amounts of ketones and betahydroxybutyric were always found in the urines of these normal children when their caloric requirements were fully covered by the diet. The amount was small and varied from 20 to 100 mg. in terms of acetone in twenty-four hours. The average amount excreted was from 50 to 80 mg.

The age, sex, and body weight of the child apparently had no effect on the amount. As a rule the amount of betahydroxybutyric acid was somewhat greater than the amount of ketones, but this did not always hold true. We must regard these substances as present in small amounts in the urine of normal children. The large quantity of "acetone bodies" in the urine in febrile conditions and on restricted diets is due to the increase of substances normally present, rather than to the appearance of abnormal substances.

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THE SECRETION OF BILE IN ICTERUS NEONATORUM *

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About four years ago I undertook a study of icterus neonatorum by means of the duodenal catheter,¹ for it seemed as if a method of obtaining bile at the site of entry into the intestine offered advantages over methods hitherto employed. Accordingly a considerable number of infants, some 124 in all, were tested by this means, and observations were made as to the onset of the excretion of bile in the new-born, its relation to the intake of colostrum, and especially as to its association with jaundice. The details of the various cases comprising this investigation will be found in the paper referred to. The results may be broadly summarized in a short table (Table 1).

In order to determine the onset of the excretion of bile, tests were carried out day after day for a period of several days on each infant, the aspiration being continued for two ten-minute periods. First, a number of unselected infants were examined, and later a group chosen on account of early or marked icterus. The conclusions drawn from these tests were: that bile is very rarely excreted during the first twelve hours of life; that its secretion in the subsequent days is variable, being more profuse in cases with marked jaundice; that when jaundice manifests itself, it precedes the excretion of bile into the duodenum; that secretion varies within wide limits; and that the occurrence of jaundice results from a defective correlation of excretion and secretion, it being generally caused by the inability of the rudimentary excretion to cope with the sudden profuse secretion of bile.

About a year after the publication of this paper, Ylppö² published a most interesting article on this subject, regarded from an entirely new point of view. He carried out spectrophotometric examinations of the blood, urine and stools in icterus neonatorum, and in this way determined the amount of bile pigments which they contained. His conclusions relating to the occurrence of bile in the stools may be summarized as follows: first, that there is an increased secretion of bile after birth, augmenting gradually during the first five "critical days" until about the sixth day, when there is again a marked rise in the volume of bile secreted; second, that there is no difference between the icteric and the

* Submitted for publication Feb. 4, 1916.

1. Hess, A. F.: *AM. JOUR. DIS. CHILD.*, May, 1912, p. 304.

2. Ylppö, A.: *Ztschr. f. Kinderh.*, 1913, Orig., ix, 208.

nonicteric infant in the amount of secretion or excretion of bile. Ylppö has represented in the form of curves the gradual rise during the first five days of life, as well as the sudden rise occurring at the end of this period; five curves of this kind are depicted, based on the examinations of eleven infants.

These conclusions—the definite curve of secretion and excretion, as well as the relation of bile excretion to icterus—are, it will be noted, in conflict with the results previously obtained by me, and it is for this reason that I have returned to this subject, especially as this paper has been reviewed in a recent number of this journal.³ During the past two years, in view of Ylppö's statements, I have availed myself of numerous opportunities to repeat these tests of the new-born, and have obtained the same results as before and been led to the same conclusions.

TABLE 1.—RELATION OF AGE TO EXCRETION OF BILE (DUODENAL CATHETER)

No. of Cases	Age	No Bile	Bile	Marked Jaundice	Remarks
52	½ to 12 hours.....	51	1	0	Thirty-nine infants were less than 6 hours old.
19	12 to 36 hours.....	15	4	4	Marked jaundice in all four positive cases; in others no bile obtained.
15	1½ to 3 days.....	5	10	6	Marked jaundice in four positive cases; in other two jaundiced cases, bile next day.
13	3 to 4 days.....	4	9	6	Jaundice not increasing.
12	4 to 5 days.....	2	10	5	Jaundice decreasing.
13	6 to 11 days.....	2	11	4	Jaundice decreasing.

Before entering into an analysis of the data, in order to attempt to explain the conflicting opinions, we must realize that examinations of the stool furnish merely an indirect method of determining excretion of bile, and that they presuppose something which is by no means certain, namely, that no bile is reabsorbed by the intestine. Tests by means of the duodenal catheter, on the other hand, are not open to this criticism.

At the very outset let me say that I believe it is not possible to construct a reliable curve representing bile excretion in the new-born, and that I relinquished as fruitless such an attempt at the time of writing the previous article. If the degree of secretion were to be depicted graphically, it would not constitute a gradually rising curve, but an irregular and precipitous marking, for the secretion during the first

3. Holmes, J. B.: AM. JOUR. DIS. CHILD., January, 1916, p. 62.

twelve or twenty-four hours is very scant indeed, and generally increases rapidly during the next few days. But graphic illustration is absolutely inapplicable to this study, as in one case there may be an intense secretion of bile by the second day of life, and in others practically none until the fifth or sixth day. Reference to the tests previously reported would seem convincing on this point, for they show all manner of variations in the rate of excretion. How, then, does it come about that Ylppö described a gradually increasing wave of secretion, with a sudden exacerbation about the fifth day? This lay in the very method by which he approached the problem. At the outset he formulated four periods, the first embracing the first five days of life, the second the sixth to the eighth day, the third from the ninth to the eleventh day, and the fourth the twelfth and thirteenth days. As he found a decidedly greater amount of bile in the stool passed during the second period, which, we will remember, began with the fifth day, than that passed during the first period, he drew the conclusion that a sudden flow of bile occurred on about this day, and outlined a hypothetical curve to represent a gradually increasing secretion throughout the first period. It is evidently impossible, as has been pointed out elsewhere,⁴ to construct a curve of daily excretion by determining the bile in the total stool passed during these several periods, or to form any opinion whatsoever as to the degree of secretion or excretion for the individual twenty-four periods during the first five days of life. Nor is it possible to state that there is a sudden rise taking place at the fifth or sixth day. This method evidently allows one merely to compare the four periods one with another. Daily tests carried out by means of the duodenal catheter, however, have led me to the opinion that there is an initial lack of excretion during the first twenty-four hours or more, and that there follows a somewhat sudden rise in the outflow of bile, this increase taking place generally before the fifth day, frequently on the third or fourth day.

The second question for consideration is whether there is an increased excretion of bile more often in infants showing decided icterus than among those who manifest no signs of jaundice. Ylppö answers this in the negative. His conclusions are based on a study of ten cases, in which the amount of bile pigment was determined in the total stool passed during the first five days. The data of these cases are given in Table 2 and show the grade of icterus, the total amount of bile pigment found, and the total number of grams of stool excreted. It would seem as if ten cases were very few on which to base definite conclusions, especially when these cases must be subdivided so as to represent three clinical groups, one showing no jaundice, another moderate jaundice,

4. Hess, A. F.: *Ergeb. d. inn. Med. u. Kinderh.*, 1914, xiii, 560.

and a third marked or intense jaundice. Furthermore, it will be noted in the table that in two of the three cases in which no jaundice occurred, but in which, nevertheless, a marked excretion of bile took place, the amount of stool obtained during this period was exceptionally large, indeed, two or three times the number of grams collected in many of the other cases. This is difficult to understand, and certainly renders these cases unsuitable for the purpose of comparison, for we should expect to obtain an abnormal amount of bile under such circumstances.

TABLE 2.—RELATION OF BILE EXCRETION TO STOOL PASSED DURING FIRST FIVE DAYS OF LIFE. (YLPPÖ'S CASES.)

Case No.	Grade of Icterus	Total Bile in Stool in First Five Days, Mg.	Total Stool, Gm.	Remarks
1	Negative	28.16	16.09	Immense quantity of bile pigment excreted in next two days (57.83 gm.).
2	Marked	8.28	3.22	
3	Moderate	39.79	4.72	
4	Moderate	21.13	2.98	
5	Negative	43.89	5.72	
6	Moderate	29.95	9.63	
7	Negative	32.77	13.42	
8	Very marked	21.70	12.85	
9	Slight	33.85	6.50	
10	Marked	28.84	19.10	

It is quite true that there is no absolute parallelism between bile excretion and jaundice. Cases previously reported illustrate the occasional occurrence of a wide divergence in these respects. For example, we have noted a high degree of jaundice accompanied by an excessive secretion of bile; no secretion of bile, and almost an absence of jaundice during the first five days of life; and an instance showing marked jaundice on the fourth day, but no secretion of bile until two days later. These cases, however, constitute the exceptions. If we examine a hundred or more cases, more particularly if we select a number of infants on account of the occurrence of marked jaundice, we shall find that an excessive excretion of bile is associated more often with a marked than with a faint degree of jaundice. This will be more especially the case if the duodenal tests are carried out between the second and fifth day, when the excretion has been well established and the icterus has begun to recede.⁵

5. It is difficult to conceive how it will be possible to estimate the daily excretion of bile during life by any method other than duodenal tests. The only other possible means of access would seem to be a fistula.

The amount of bile flow and the icterus do not depend on one factor, but on two—secretion and excretion. This is well illustrated by some cases of congenital obliteration of the bile ducts described by Still⁶ and also by Thompson,⁷ in which, in spite of the absolute obstruction, there was no jaundice for some weeks owing to the lack of secretion. When jaundice is intense, however, the secretion of bile cannot be wanting, and we are more apt to encounter it in plenty in the duodenum than to find it deficient. In cases selected on account of marked jaundice, bile was frequently found in the stomach by means of a stomach tube, or appeared with regurgitated colostrum, owing to the fact that its marked alkalinity tended to a relaxation of the pyloric sphincter. In the most marked case which we met with, in which the infant assumed a saffron color, there was an almost constant welling forth of bile into the stomach.

CONCLUSIONS

In conclusion we may state that the amount of bile-flow during the first twelve to thirty-six hours of life is very scanty, and that, although it then increases in volume, it is subject to wide fluctuations. It is therefore inaccurate to depict it graphically, as has been attempted, as a gradual rise dating from the time of birth. To quote from our previous paper: "The secretion of bile varies within wide limits. In general it is marked when jaundice is marked."

Furthermore, recent investigations of icterus neonatorum seem to confirm the interpretation that "the occurrence of jaundice results from a defective correlation of excretion and secretion, and is generally caused by the inability of the rudimentary excretion to cope with the sudden profuse secretion of bile."

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6. Still, G. F.: *Clin. Jour.*, 1901, xvii, 323.

7. Thompson, J.: *Congenital Obliteration of the Bile Ducts*, 1902.

CLINICAL DEPARTMENT

A CASE OF SECONDARY HYPERTROPHIC OSTEO-ARTHROPATHY IN A GIRL 11 YEARS OLD*

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Although 144 cases of secondary hypertrophic osteo-arthritis have been reported, only seven of these occurred in children. The following case, therefore, seems worthy of being reported:

REPORT OF CASE

History.—B. B., aged 11½. There is no history of tuberculosis or syphilis in the family. The parents have been married twenty-two years and have had eight children. The eldest, now 21 years old, is married and has two healthy children. There have been no deaths and the mother has had no miscarriages or stillbirths. None of the other children have had any symptoms pointing to tuberculous or syphilitic disease of the lungs, bones or lymph nodes. The patient was breast fed for one year, began to walk at the age of 1½ years, and had measles at 2 years. She was always weaker than the other children. When she was 7 years old, the mother noticed that she held her head to one side and did not stand straight. At this time she had been associating with a girl in the neighborhood who had hip disease and was wearing a plaster dressing. The spinal curvature became rapidly more marked. In 1912, when 8 years old, she was admitted to the Hospital for the Ruptured and Crippled and a Hibb's operation was performed by Dr. Whitman. At the time of the operation there was no distinct evidence of tuberculosis and no spasm, but only a marked limitation movement, such as was evidently due to the ankylosis and the resulting deformity of the spine. The child improved during the following year, but has grown worse during the last two years. At one time there were symptoms of paraplegia and the patellar reflexes were exaggerated. Roentgenologic examination at the time showed that there was destruction of the bodies of the fifth, sixth and seventh dorsal vertebrae, with very marked deformity of the spine. During the past four years she has lost weight, has had a cough, which is worse at night, but has not had night sweats. The enlargement of the ends of the fingers was first noticed seven months, and that of the knees and ankles about four months, prior to examination, and that of the wrists and joints of the fingers only a few weeks previously. There has been pain, not very severe in the knees, ankles and fingers.

Examination.—The patient was admitted to the Lebanon Hospital, September 1, 1915, at which time she weighed 49 pounds, was poorly nourished, anemic, and had marked curvature of the spine with pronounced deformity of the chest (Fig. 1). The nose appeared large and broad and the jaw prominent. There was dyspnea which became more marked after slight exertion. On account of the deformity of the chest the examination of the lungs was difficult. The heart sounds were normal. There were fine râles heard

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in the axillary line and over both bases posteriorly. The patient complained of pain on both sides of the chest, more intense on coughing or deep inspiration. There was a small quantity of mucopurulent expectoration; large quantities were never present; it was never foul-smelling and examination on two occasions failed to show the presence of the tubercle bacillus. The von Pirquet cutaneous reaction, however, was positive. The Wassermann reaction was negative. There was distinct atrophy of the muscles of the arm (Fig. 1), the wrists were enlarged, the hands were cold but not cyanotic, the joints of the fingers slightly swollen, and the ends distinctly clubbed (Fig. 2). Examination of the abdominal organs presented nothing abnormal. The circumferences of the knee (Fig. 3) and ankle joints were increased and there was some



Fig. 1.—Author's patient, showing broad nose, prominent jaw, deformity of the chest and atrophy of the muscles of the arm.

atrophy of the muscles of the leg. The patient's temperature ranged between 99 and 101.2 F. The urine contained a small amount of albumin but no casts. During her stay in the hospital (two weeks) the patient gained 1 pound.

Roentgenologic examination of the hand (Fig. 4) showed a deposit of a thin layer of newly formed bone under the periosteum of the metacarpals and a similar but less distinct layer in the first phalanges. At the ends of the terminal phalanges small "burr-like" projections were noted. The joints of the fingers and the wrist showed no changes. Similar changes were seen in the metatarsal bones of the foot and the terminal phalanges, especially the last phalanx of the middle toe (Fig. 5). The knee (Fig. 6) showed a similar

subperiosteal deposit over the lower end of the femur and the upper end of the tibia and fibula. No changes in the knee joint itself were noted. Similar deposits of newly formed bone were found over the lower end of the radius and the ulna and the lower portion of the tibia and the fibula.

According to Locke,¹ 144 cases of secondary hypertrophic osteoarthropathy, including his own, have been reported. Of these only seven occurred in children.²

In adults, the condition occurs five times as often in men as in women, and most of the patients are between 20 and 40 years of age. It is always secondary; some form of chronic disease of the lungs is present in 78 per cent. of the cases, the most frequent lesion being bronchiectasis, which is nearly always present in the most marked cases. Pulmonary tuberculosis is present as an etiologic factor in 20 per cent., and empyema is next in frequency. One of the most plausible explanations as to the cause of the changes in the bones and other tissues is that the imperfect function of the lungs causes a lack of proper elimination of toxic substances; these being absorbed into the circulation, cause changes where the circulation is slowest, namely, in the distal parts. Occasionally similar changes follow certain diseases

1. Locke: Secondary Hypertrophic Osteo-Arthropathy and Its Relation to Simple Club Fingers, with a complete bibliography, *Arch. Int. Med.*, 1915, xv, 659.

2. Bamberger: (*Ztschr. f. klin. Med.*, Berl., 1891, xviii, 193) Boy, aged 7 years; chronic pulmonary tuberculosis; typical findings at postmortem examination. Davis: (*Jour. Am. Med. Assn.*, 1895, xxiv, 845) Boy, aged 4½ years; empyema communicating with a bronchus; typical report. Hall: (*Edinburgh Med. Jour.*, 1905, New Series 18, lx, 127) Boy, aged 14 years; sarcoma of the lung and sarcoma of the femur; typical postmortem findings. Lockwood: (*Tr. Clin. Soc. London*, 1897, xxx, 133) Girl, aged 10 years; chronic pulmonary tuberculosis; spinal caries; description typical. Rendu and Boulloche: (*Bull. et mém. Soc. méd. d. hôp. de Paris*, 1901, xviii, 127) Boy, aged 11 years; empyema; attacks of pain and swelling of the joints without rise of temperature; typical roentgenograms. Thompson: (*Tr. Med.-Chir. Soc. London*, 1904, lxxxvii, 85) Girl, aged 10 years; chronic engorgement of the lung; spondylitis; amyloid disease; typical roentgenograms. Whitman: (*Pediatrics*, 1899, vii, 154) Girl, aged 8 years; chronic pulmonary tuberculosis, spondylitis, bones tender; typical roentgenograms. To these the following more or less atypical cases may be added: Gilbert and Fournier: (*Rev. mens. d. mal. de l'enf.*, 1895, xiii, 309) Child, aged 13 years; hypertrophic biliary cirrhosis; no disease of the lung; swelling of the bones near the knee; pain in the wrist, clubbing of the fingers. Child, aged 13 years; hypertrophic biliary cirrhosis; no disease of the lungs; enlargement of the ends of the tibia; pain and swelling of the knee; clubbing of the fingers. The following cases showed clubbing of the fingers without changes in the bones: Moizard: (*Bull. et mém. Soc. med. d. hôp. de Paris*, 1893, x, 359) Boy, aged 6 years; pneumonia and empyema. Girl, aged 5 years; pneumonia and empyema. Marfan: (*Bull. et mém. Soc. méd. d. hôp. de Paris*, 1893, x, 365) Child with empyema; child with bronchiectasis; child with cystitis and pyelonephritis. Bécclère: (*Bull. et mém. Soc. d. hôp. de Paris*, 1901, xviii, 283) Child with aneurism of the subclavian artery; clubbing of the fingers of one hand; no changes in the bones.

of the liver, the disturbed function of the organ resulting in imperfect elimination. The characteristic feature of the condition is the deposit of a thin layer of new bone under the periosteum, more marked in certain bones, namely, the lower end of the radius and ulna, the lower end of the tibia and fibula, the metacarpals, the metatarsals, and the first

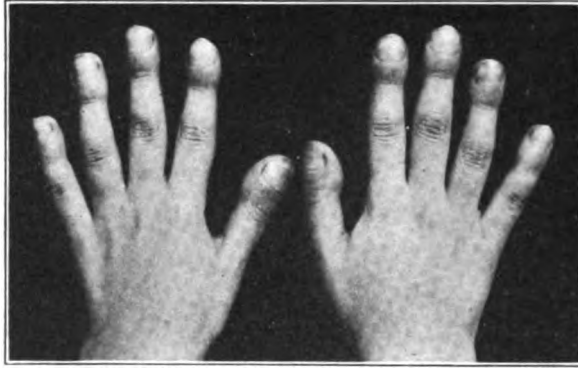


Fig. 2.—Showing clubbing of the fingers and slight swelling of the joints of the fingers.

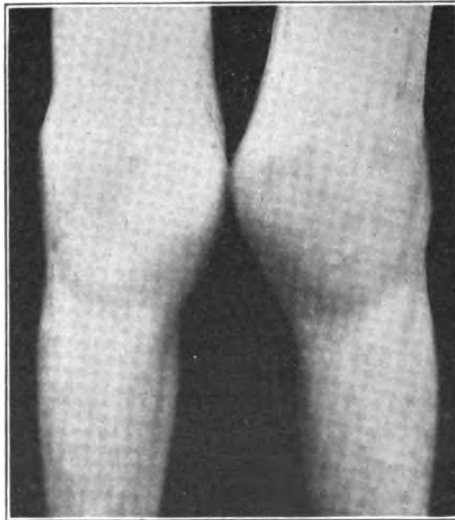


Fig. 3.—Showing enlargement of the knee joints.

phalanges of the hands and feet ; somewhat less distinct in the humerus, femur, upper end of radius, ulna, tibia, fibula, clavicle, acromion process, ribs and iliac crest. A careful roentgenologic study in well-marked cases shows that nearly all the bones are affected. In such cases the epiphyses may also show irregular deposits. This layer of newly



Fig. 4.—Showing deposit of layer of newly formed bone on the metacarpal bones and first phalanges, and burr-like proliferation on the distal half of the terminal phalanges.



Fig. 5.—Showing deposit of layer of newly formed bone on the metatarsal bones and burr-like proliferation on the terminal phalanx of the middle toe.



Fig. 6.—Showing layer of newly formed bone on the lower end of the femur and the upper end of the tibia and fibula. The joint itself is apparently normal.

formed bone which is most distinct at the lower end of the shaft begins a couple of inches above the joint and stops at the edge of the cartilage. According to Locke the process is a slowly progressive ossifying periostitis. At first this periosteal layer is sharply defined, but after a couple of years it has a tendency to fuse with the underlying parts, so that it becomes less distinct. The roentgenologic examination in the late stages shows a decrease in the density of the shaft. The clubbing of the fingers is due largely to changes in the soft parts, but the terminal phalanges frequently show a "burr-like" proliferation in their distal half and occasionally osteophytes (Fig. 4). The joints usually show no changes, but in severe cases there may be thickening of the periarthritic tissue, slight effusion, and erosion of the cartilage.

An interesting and important question is the relation of cases of simple clubbing of the fingers to cases of secondary hypertrophic osteo-arthropathy. Locke believes that the conditions are identical, the former representing an early stage of the latter. He bases his opinion primarily on the fact that in a series of thirty-nine cases of simple clubbing, eleven, or 28 per cent., showed, roentgenologically, changes in the long bones similar to those seen in osteo-arthropathy. The fact that 72 per cent. of the cases of simple clubbing are associated with pulmonary disease, and 50 per cent. with pulmonary tuberculosis, is also suggestive. In my own case the clubbing of the fingers was the first manifestation of changes in the extremities.

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No. 5

ACIDOSIS OCCURRING WITH DIARRHEA *

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During the course of attacks of severe diarrhea, not of the ileocolitis type, in infants, alterations in the respiration are not infrequently encountered. The usual abdominal type of respiration of the young child is succeeded by one which is both costal and abdominal. The most striking feature is the amplitude of the respirations and the distinct effort with which they are accomplished. They are heaving, the thorax being often greatly elevated and depressed and the accessory muscles of respiration brought into play. There is no evidence of obstruction and no cyanosis. The frequency of the respiration is usually increased but not greatly so. Sometimes there is a greater or less alteration of the depth of the individual respirations so that a modified Cheyne-Stokes type results, but in general the excursions of the thorax and abdomen are nearly the same with succeeding respirations. This increased pulmonary ventilation or hyperpnea may go on uninterruptedly for many hours. Eventually, in fatal cases, the respirations become feebler and feebler with only occasional deep gasps, and finally they cease altogether. It is as if the respiratory center were exhausted by the exertions which it has undergone.

Czerny¹ was, we believe, the first to describe this alteration in the character of the respiration in nutritional conditions. He called attention to the resemblance between the respiration of infants dying of gastro-intestinal disease and that of rabbits poisoned with mineral acids.

The object of the present communication is to give in some detail observations which have enabled us to demonstrate that the hyperpnea in many cases of severe diarrhea² is associated with, and dependent on, the presence of acidosis.

* Submitted for publication, March 15, 1916.

* From the Harriet Lane Home and the Department of Pediatrics of the Johns Hopkins University.

1. Czerny: *Jahrb. f. Kinderh.*, 1897, xlv, 271.

2. Preliminary reports on this subject have been made in the Proceedings of the Society for Experimental Biology and Medicine, 1914, xii, 51, and in The Bulletin of the Johns Hopkins Hospital, 1916, xxvii, 63.

The term "acidosis" has been used in connection with nutritional disorders ever since it was first shown by Keller³ that in such disorders there is to be found at times a great increase of the ammonia coefficient (ammonia nitrogen to total nitrogen). Using a very inexact method (Schlössing's), he determined that the ammonia coefficient of infants varied between 2 and 57 per cent. With Czerny, Keller⁴ pointed out that an increase of fat in the food produced in some patients a rapid and marked increase of the actual and relative amount of ammonia excreted in the urine. Numerous observers have substantiated these findings. It has been sufficiently shown, however, that even a very marked amount of fat may not produce such a change. Thus Howland and Cooke⁵ fed to an infant of 10 months a diluted cream mixture containing about 7 per cent. fat. The amount of fat ingested each day was 76 gm. With this food there was no increase of ammonia. In two other children there was no increase of ammonia excretion until marked diarrhea occurred. Such has been the experience also of others. Amberg and Morrill⁶ have shown that in a normal infant an increase of fat in the food is without effect on the ammonia coefficient if the amount of protein remains constant. Czerny and Keller⁴ insisted on the dependence of increased ammonia excretion on the condition of the child; it occurred when there was evidence of gastro-intestinal disturbance. It is with the presence of diarrhea chiefly that the ammonia coefficient is increased. This has been a very general, almost a regular, finding.

To account for the excess of ammonia, Keller looked for abnormal acids but was not able to prove their presence. Steinitz⁷ determined a mineral loss by the intestine and believed that it was the mineral loss (especially the loss of sodium) that made necessary an increase of ammonia to compensate for the deficiency of bases in the blood and tissues. This acidosis was, therefore, to be considered as relative, inasmuch as it was not due to excessive acid production.

While this increase of ammonia, due to whatever cause, has been spoken of as acidosis, the acidosis has not usually been considered an important or threatening condition. Steinitz emphasized the loss of base as the all-important matter and specifically mentioned the danger as one accruing from a long-continued loss of base. His title "*Zur Kenntnis der chronischen Ernährungsstörungen der Säuglinge*" makes

3. Keller: *Jahrb. f. Kinderh.*, 1897, xlv, 25.

4. Czerny and Keller: *Jahrb. f. Kinderh.*, 1897, xlv, 274.

5. Howland and Cooke: *Tr. Am. Ped. Soc.*, 1910, xii, 130.

6. Amberg and Morrill: *Jahrb. f. Kinderh.*, 1909, lxix, 280.

7. Steinitz: *Jahrb. f. Kinderh.*, 1903, lvii, 689. It may be pointed out here that Steinitz' contention presupposes that the alkali lost (chiefly sodium) is potential alkali and not merely a neutral salt. This has never been proven and is absolutely necessary for the substantiation of his hypothesis.

this sufficiently clear. Czerny⁸ alone, apparently, has emphasized the immediate importance of the acidosis which was believed by him on the basis of Steinitz's work to be due to the loss of alkali. He thought that an explanation had thus been offered for the alteration of respiration, and that the relative acidosis might be severe enough to be the cause of death.

Ludwig Meyer⁹ refused to commit himself on the importance of the acidosis (determined by an increased ammonia coefficient) on the development of "alimentäre Intoxikation." Tobler and Bessau¹⁰ have discussed at length the ammonia coefficient and the microchemical staining methods for determining acid excess in the tissues and Salge's results (to be mentioned later). They conclude:¹¹ "There is still required an answer to the question whether any particular clinical picture or any complex of characteristic symptoms such, for instance, as those of 'alimentäre Intoxikation' are found with one or the other of the various anomalies of metabolism that have here been described. According to the present standpoint of our knowledge the answer to this question must be 'No.'"

It would be going too far afield to discuss the significance of an increased ammonia coefficient. It is found in a great variety of conditions in which there is no other evidence of acidosis, and in such conditions as nephritis it is not a necessary accompaniment of acidosis. What should be emphasized is the fact that no sufficient evidence of the presence of acidosis has ever been brought forward, and that although acidosis has been spoken of in connection with nutritional disturbances, there has been no suggestion by anyone but Czerny that in the diarrheal diseases of infancy there may develop rapidly a severe and usually fatal acidosis not due to the production of acetone bodies. So far as we are aware, no one has made a practice of treating the acidosis with alkalies.

8. Czerny and Keller: Die Ernährung des Kindes, Ernährungsstörungen und Ernährungstherapie, Vol. 2, p. 161.

9. Meyer: Jahrb. f. Kinderh., 1907, lxxv, 608. "Es wäre verfrüht, heute, wo wir erst im Beginn der Forschung der Stoffwechselstörungen bei Intoxikationen stehen, etwa die markanteste Alteration des Stoffwechsels, die wir bei der Intoxikation beobachten konnten, die Acidose, als Ursache des Zustandes anzusprechen."

10. Tobler and Bessau: Allgemeine pathologische Physiologie der Ernährung und des Stoffwechsels im Kindesalter, Wiesbaden, 1914.

11. "Es bedarf noch die Frage der Beantwortung, ob irgend ein bestimmtes Krankheitsbild oder ein Komplex charakteristischer Symptome, wie etwa derjenige der sog. 'alimentären Intoxikation,' mit der einen oder anderen der hier besprochenen Stoffwechselanomalien zusammenfällt. Nach dem derzeitigen Stand unserer Kenntnisse muss diese Frage verneint werden."

Salge¹² investigated, by means of the electrical method, the hydrogen ion concentration of the blood serum in ten normal infants and in a five weeks old infant with *Intoxikation*. He found the hydrogen ion concentration of the serum of the normal infants to vary between $10^{-7.2}$ and $10^{-7.63}$. That of the infant with *Intoxikation* was $10^{-4.84}$. In a subsequent communication¹³ he reported one more case of *Intoxikation* in which the hydrogen ion concentration of the serum was $10^{-6.2}$. The accuracy of the determinations is seriously to be questioned, first, on account of the wide variations among the normal, and second, because of the virtual impossibility of ever finding such strongly acid serums during life. A concentration of $10^{-4.84}$ is one hundred times that of the maximum ever before reported, even in moribund animals poisoned with acids or in patients with diabetic coma, and a concentration of $10^{-6.2}$ is probably much greater than can ever occur in life.

CARBON DIOXID TENSION IN THE ALVEOLAR AIR

The disturbance of respiration (hyperpnea) occurring in many cases of severe diarrhea is such as to suggest that the respiratory center is strongly stimulated. This stimulation is due to an increase in the hydrogen ion concentration of the blood, *i. e.*, to a shifting of the reaction of the blood in the direction of acidity, though the blood always remains alkaline. Three years ago, therefore, we tested the blood of several infants suffering from diarrhea and hyperpnea, by the method devised by Sellards, and found a complete absence of color in the evaporated protein-free filtrate of the serum to which phenolphthalein had been added. Such a reaction as this is known to occur in cases of severe acidosis. On the basis of this information we have undertaken a systematic study of the whole question with the available methods. We have determined the tension or effective concentration of the carbon dioxide in the alveolar air. In acidosis there is a reduction of the carbon dioxide tension of the alveolar air which is roughly proportional to the severity of the acidosis. It was necessary, therefore, for us to establish figures for the carbon dioxide tension of the alveolar air of normal infants and to compare with these the results obtained in cases of infants suffering from diarrhea.

So far as we are aware, the carbon dioxide tension in the alveolar air of infants has not previously been determined, probably on account of the difficulty of collecting a sample, since in most methods devised for this purpose a certain amount of cooperation on the part of the

12. Salge: Ztschr. f. Kinderh., Orig., 1912, iv, 92.

13. Salge: Ztschr. f. Kinderh., Orig., 1913, vii, 292.

patient is necessary. The Plesch method, however, as modified by Higgins¹⁴ has been successfully used on comatose adults, and we have adapted the procedure so that by the employment of a special mask it can be used for infants. The mask is made from the nipple of a wide-mouthed (Hygeia) nursing-bottle. A sheet of rubber tissue 8 by 10 inches is fastened to the lower rim of the nipple by means of rubber cement and adhesive plaster. The tip of the nipple is cut off and a short glass tube $\frac{3}{8}$ inch in diameter is inserted in its place. In making a collection of alveolar air a rubber bag of 500 c.c. capacity is connected with the mask and partially filled with air by means of an aspirator bulb. The neck of the bag is closed off with a pinch-cock or with the fingers, the mask is placed over the nose and mouth of the infant and the rubber tissue closely drawn around the face so as to prevent the escape of air. If possible, the mask should be placed over the face just at the end of expiration. Respirations are allowed to continue for from twenty-eight to thirty-two seconds, and at the end of an expiration the neck of the bag is closed off and the mask removed from the face. The air must be analyzed immediately, as diffusion occurs rapidly through the rubber and the composition of the air is altered. Analysis of the sample of air may be made with the Haldane apparatus¹⁵ or more simply, and with a sufficient degree of accuracy, by the colorimetric method.¹⁶

We have found it necessary that the infant should have been breathing quietly for one minute previous to the collection of the sample of air, since vigorous crying just before the mask is put on leads to a lowering of the carbon dioxid tension by several millimeters. Crying during the collection of the sample, on the other hand, almost invariably occurs and facilitates the gaseous exchange. If the crying is very vigorous, the effect is to raise the tension somewhat, but not to such an extent as to be significant.

The initial amount of air in the bag must be such that during inspiration the bag is at least one-half, and preferably, as much as two-thirds, emptied, but not completely collapsed. The amount of air required for infants under 1 year of age varies from 250 c.c. to 400 c.c.

If the foregoing simple conditions are complied with, duplicate determinations usually agree within 2 mm. More than one determination should always be made, especially in confirmation of a low tension, as errors in technic usually lead to low figures. If the time of collection exceeds 32 seconds, too high a result is obtained.

14. Boothby and Peabody: *Arch. Int. Med.*, 1914, xiii, 497.

15. Haldane: *Methods of Air Analysis*, London, 1912.

16. Marriott: *Jour. Am. Med. Assn.*, 1916.

In a series of normal infants the carbon dioxid tension in the alveolar air has been found to vary from 36 to 45 mm., as is shown in Table 1.

TABLE 1.—CARBON DIOXID TENSION IN THE ALVEOLAR AIR OF NORMAL INFANTS

Case	Tension, mm.	Case	Tension, mm.	Case	Tension, mm.
I	43.3	X	38.4	XVII	37.3 39.8
II	42.3	XI	38.4	XVIII	39.2
III	44.5 43.2	XII	38.8 42.2 45. 45.5	XIX	38.6 38.2
IV	43. 43. 45.7	XIII	38.6 40. 43. 40.	XX	39. 40.7
V	37.7 37.4	XIV	39.6 41.8	XXI	38.1
VI	38.2 36.2	XV	41.4 43.	XXII	39.3
VII	39.6	XVI	40. 38.4 38.8	XXIII	37.8
VIII	37. 38.2 37.			XXIV	45.8
IX	37.4			XXV	43.2
				XXVI	38.
				XXVII	41.8

It will be seen that the figures fall within rather narrow limits. Several determinations on the same patient, often weeks apart, give nearly the same results. It is immaterial whether we determine the actual carbon dioxid tension of the alveolar air. What we wish to obtain is results that are nearly uniform in the normal child and that can be used for comparison with the sick.

A lowered tension of carbon dioxid is to be considered an indication of acidosis.¹⁷

In a considerable number of our cases of diarrhea, and in all cases of diarrhea in which an unmistakable hyperpnea was present,

17. For a discussion of the significance of carbon dioxid tension in the alveolar air, see Peabody: *Am. Jour. Med. Sc.*, 1916, cli, 184. Howland and Marriott: *Bull. Johns Hopkins Hosp.*, 1916, xxvii, 63. The method should not be applied to patients suffering from pulmonary complications. The administration of large quantities of caffeine results in a lowering of the carbon dioxid tension; morphin exerts the opposite effect.

we have found a lowered tension of carbon dioxide in the alveolar air. The administration of an alkali to these patients has been followed by a cessation of the hyperpnea and a coincident return of the carbon dioxide to a normal or even abnormally high tension. Illustrative examples are given in Table 2.

TABLE 2.—CARBON DIOXIDE TENSION IN THE ALVEOLAR AIR OF INFANTS WITH ACIDOSIS

Case	Date	Carbon Dioxide, mm.	Hyperpnea	Alkali
I	9/22	21.2	+++	Given
	9/23	42.0	0	Given
	9/24	54.0	0	Stopped
	9/24	55.0	0	
	9/25	41.3	0	
II	9/28	18.0	+++	Given
	9/28	17.8	+++	Given
	9/29	21.3	++	Given
	9/30	32.8	+	Given
III	9/27	27.0	++	Given
	9/28	34.0	+	Given
	9/29	36.0	0	Given
IV	11/16	32.8	+	Given
	11/17	36.8	+	Given
	11/20	59.0	0	Stopped
	11/24	48.2	0	
	12/ 2	44.8	0	
V	27.8	++	
VI	30.4	++	
VII	24.4	+++	
VIII	27.0	++	
IX	4/16	28.8	+	Given
	4/17	33.	0	Given
X	25.2	++	
XI	21.	+++	
XII	14.3	+++	

HYDROGEN ION CONCENTRATION OF THE SERUM

Changes in the hydrogen ion concentration of the blood serum were determined by the dialysis indicator method devised by Levy, Rowntree and Marriott¹⁸ with the modification later suggested by

18. Levy, Rowntree and Marriott: Arch. Int. Med., 1915, xvi, 389.

Marriott.¹⁹ This gives the concentration of the serum as it is first obtained and after the carbon dioxide has been driven off by blowing. The latter figure is the more valuable index of acidosis as it allows of comparison under perfectly definite and constant conditions and is an indication of the effective alkali reserve. We have not found the hydrogen ion concentration of the serum of normal infants with its contained carbon dioxide to go beyond 7.4.²⁰ After removing the carbon dioxide, we have found it between 8.4 and 8.5. We have found that infants with diarrhea, hyperpnea and other evidence of acidosis often have a greatly increased hydrogen ion concentration of the serum. In severe cases, we have found it to be as great as 7.2 before

19. Marriott: Unpublished work.

20. The following description of physico-chemical notation is taken from the article by Levy, Rowntree and Marriott: *Arch. Int. Med.*, 1915, xvi, 390.—“A solution is acid when it contains an excess of hydrogen over hydroxyl ions, neutral when hydrogen and hydroxyl ions are in equal numbers, and alkaline when hydroxyl ions predominate. An acid of ‘normal’ strength contains, in 1 liter, a gram of hydrogen capable of forming hydrogen ions, and its strength may be expressed as 1 N. Diluting such a solution ten times, we would have 1/10 N or a solution containing 1/10 gram of actual or potential hydrogen ions to the liter. Continuing the process of dilution until 1/10,000,000 normal acid is obtained, we would have in such a solution 1/10,000,000 gram of hydrogen ions. Pure water, however, dissociates to form hydrogen and hydroxyl ions, and at 200 C. contains approximately 1/10,000,000 gram of hydrogen ions to the liter and an equivalent amount of hydroxyl ions. That is to say, pure water, our standard of neutrality, is 1/10,000,000 N acid and also 1/10,000,000 N alkaline. To avoid writing large figures it is customary to use logarithmic notation and to express 1/10,000,000 N as 10^{-7} N or, more conveniently, as suggested by Sørensen, to drop the 10 and minus sign and say pH7. If we have less than 1/10,000,000 gram of hydrogen ions to the liter, the solution is less acid than water, that is, it is alkaline—so, pH8 means actually 1/1,000,000 N alkaline. The higher the exponent the more alkaline, or what is saying the same thing, the less acid is the solution.

To sum up:

pH1 — N/10 acid
 .
 .
 .
 pH6 — N/1,000,000 acid
 pH7 — Neutrality
 pH8 — N/1,000,000 alkali
 .
 .
 .
 pH14 — N/10 alkali

(Ch7, pH7 and $(H^+) = 7$ are synonymous expressions. Intermediate values, as for example, between pH7 and pH8, are commonly expressed in one of two ways, as 0.25×10^{-7} or pH — 7.6. The latter method is used in this paper. The conversion of one expression into the other is simple. For example, $\log. 0.25 = -0.602$, then $0.25 \times 10^{-7} = 10^{-0.602} \times 10^{-7} = 10^{-7.602}$ or pH = 7.602.)”

removal of the carbon dioxid and to change only to 7.5 after removal of the carbon dioxid. A number of our results are shown in Table 3.

TABLE 3.—HYDROGEN ION CONCENTRATION OF SERUM IN ACIDOSIS

Case	With Carbon Dioxid	Without Carbon Dioxid
I	7.75	8.15
II	7.5	8.1
III	7.3	7.6
IV	7.2	7.5
V	7.2	7.55
VI	7.25	7.45
VII	7.3	7.9

SELLARDS' TEST

We have examined the sera of normal infants and of those in whom we had reason to suspect acidosis, by the method devised by Sellards.²¹ This consists in evaporating the protein-free alcoholic extract of the blood serum to dryness with a few drops of phenolphthalein. Under normal circumstances, or, unless acidosis is present, a deep reddish purple color develops as evaporation proceeds, and the residue is purple and remains so. With many of our cases of severe diarrhea with hyperpnea the color was light pink or entirely lacking, though it sometimes developed on the addition of water. This alteration in behavior is to be taken as an evidence of acidosis of a marked degree of severity and probably indicates a serious diminution of the alkali reserve of the blood.²² When sodium bicarbonate was given in sufficient quantity by mouth or intravenously, the color appeared after evaporation in the same manner as with normal patients.

In a number of our patients, the tolerance for alkalis (that amount which causes a distinct alteration in the reaction of the urine) has been determined. With normal infants 2 or 3 gm. of sodium bicarbonate are usually sufficient to bring about an alkaline reaction of the urine to litmus and to keep it alkaline for twelve or more hours. With acidosis, as was shown by Sellards²¹ and later by Henderson and Palmer,²³ the amount of alkali must be greatly increased in order to bring about a similar change. An increased alkali tolerance is thus

21. Sellards: Bull. Johns Hopkins Hosp., 1914, xxv, 147.

22. Our observations were made before the introduction of the van Slyke apparatus for determining the alkali reserve of the blood. We have not used it with diarrheal cases up to the present time.

23. Henderson and Palmer: Arch. Int. Med., 1913 xii, 153.

to be looked on as an evidence of acidosis. With several of our patients, it was observed that four, five and even ten times the usual amount was necessary to alter the reaction of the urine.

HEMOGLOBIN DISSOCIATION CURVE

In confirmation of the other findings indicative of acidosis, we have studied the oxygen-combining power of the blood of our patients suffering from severe diarrhea.²⁴ Barcroft²⁵ has shown that the amount of oxygen combined with hemoglobin when it is saturated with oxygen at a given low tension is dependent on the hydrogen ion concentration of the mediums in which the hemoglobin is dissolved. With increasing acidity less oxygen is combined. If a normal blood is exposed to oxygen at a tension of 17 mm. in the absence of carbon dioxide, the hemoglobin is from 70 to 80 per cent. saturated. In our cases, with other evidences of acidosis, the hemoglobin under the same conditions has been only from 15 to 25 per cent. saturated. The hemoglobin dissociation curve is influenced by factors other than acidosis, for example, by salt concentration. Taken in connection with the other findings, however, the low dissociation curve may be considered as valuable confirmatory evidence of the presence of acidosis. Yllpö²⁶ determined the dissociation curve for the blood of infants suffering with nutritional disorders and found that the curve was normal except that just before death it was such as to indicate a severe acidosis. In our cases, however, we have frequently determined the presence of acidosis several days previous to death, and in some instances we have found unmistakable evidences of acidosis in patients who have subsequently recovered. The acidosis described in this present paper is not a terminal manifestation.

Theoretical objections might be raised against almost any of the methods available for the detection of acidosis. Realizing the possibility of experimental error to be greater than in most of the usual analytical proceedings, we have confirmed the presence of acidosis and have determined its degree by more than one method in all of our cases and have found a remarkable agreement in the results, both qualitatively and quantitatively. This is, in itself, proof of the acidosis and of the accuracy of the individual methods for its detection and quantitative determination.

It should be especially emphasized that acidosis does not occur in all cases of severe diarrhea. The majority of infants do not show evidences of it clinically or by the laboratory tests. It appears usually

24. We are indebted to Mr. H. L. Higgins for carrying out these determinations.

25. Barcroft: *Respiratory Function of the Blood*, Cambridge, 1914.

26. Yllpö: *Deutsch. med. Wchnschr.*, 1915, xli, 782.

in illnourished children who have suffered somewhat recently from one or more attacks of digestive disturbance. Finally, a severe attack of diarrhea is precipitated and acidosis results. The clinical expression of the acidosis is hyperpnea. It is not always easy to determine by observation alone whether there is increased pulmonary ventilation. For this reason, slight hyperpnea may escape detection. Its severe forms can hardly do so. When hyperpnea with diarrhea has been undoubtedly present, we have not failed to find other evidences of acidosis, but on the other hand, we have determined the presence of acidosis when the increased pulmonary ventilation was not striking.

No other symptoms, so far as we have observed, are invariably associated with the acidosis in diarrhea. Very characteristic, however, are pallor and an ashen gray color of the skin in the absence of cyanosis, great restlessness gradually giving way to stupor and eventually coma, a markedly irregular temperature curve, a polymorphonuclear leukocytosis and, especially to be emphasized, a great reduction in the amount of urine often amounting to complete anuria. A characteristic history is the following: ²⁷

An infant was breast-fed for two months and did well, gaining weight satisfactorily and having no digestive symptoms. He was then weaned and given condensed milk. At the end of one month of this feeding he suddenly became irritable and began to vomit. Four days later diarrhea began and did not yield to treatment. He was moderately developed and nourished, but showed evidences of recent loss in weight. The skin was loose, hot and very dry. His eyes were deeply sunken and staring; his color gray but not cyanotic. His mouth was dry and his lips were parched. His fontanelle was depressed. His respirations were deep, heaving, pauseless, and were accomplished with distinct effort. His heart sounds were of poor quality. His liver was enlarged. He lay usually in a semi-stupor, but when roused, was very irritable and cried with a shrill, distressed cry. His white cells were 15,000. His temperature was between 99 and 101 F. His stools were large and consisted only of a brown, watery fluid. The carbon dioxid tension of his alveolar air was 15 mm. The bicarbonate of his blood was much reduced. The reaction of his blood had changed toward acidity and the combining power of the hemoglobin for oxygen was one fourth that of the normal. The acetone bodies in his blood were not increased. Despite the administration of alkali, by mouth and subcutaneously, he died eight hours after admission to the hospital.

The symptoms of the condition are essentially those given by Finkelstein²⁸ for *alimentäre Intoxikation*. This author has insisted on the necessity for the invariable presence of nine symptoms for the diagnosis of this condition. One of these is hyperpnea (*grosse Atmung*). He has not suggested any deduction to be drawn from the hyperpnea and apparently has not appreciated its significance, for

27. Howland and Marriott: Bull. Johns Hopkins Hosp., 1916, xxvii, 67.

28. Finkelstein: Jahrb. f. Kinderh., 1907, lxx, 1.

in a later article with Meyer,²⁹ he states that "The diagnosis of *Intoxikation* was made only if the symptoms which Finkelstein has demanded were present. Most important were the stupor, the fever and the loss of weight."³⁰

CAUSE OF THE ACIDOSIS

Acidosis may result when abnormal acids are produced in excess in the body, when the kidneys fail to excrete acids normally produced, or, as Steinitz has assumed, when bases are lost from the body. We have examined the urine for the presence of acids of the acetone series, beta-oxybutyric acid and diacetic acid. As but small amounts of urine are passed, quantitative determinations of these substances have not been practicable, but qualitative tests have frequently shown no more than traces of acetone even in the presence of a severe acidosis. With acidosis due to the acetone bodies, examinations of the blood give more valuable information than examinations of the urine, as it is the acids that are retained that harm the organism and not those excreted in the urine. We have consequently determined the beta-oxybutyric and diacetic acid in the blood by the micro-method devised by one of us.³¹

We have found acetone bodies in excess of the normal amounts in the blood of these patients, but never in amounts comparable to those that are found in acidosis due to the accumulation of these substances in cases of recurrent vomiting and other conditions.³² Normally, the total acetone bodies in infants vary from 5 mg. to 15 mg. per one hundred c.c. of blood.

Associated with simple starvation in an infant 20 months old, we have seen the acetone bodies rise to 40 mg. at the end of forty-eight hours, but with no symptoms of acidosis and no appreciable alteration in the reaction of the blood. In the cases of diarrhea that have shown well-marked acidosis, the acetone bodies have varied in amount from 15 to 30 mg. per one hundred c.c. of blood, an amount entirely insufficient to account for the acidosis. In cases of ileocolitis, larger amounts of the acetone bodies may be found in the blood with a normal reaction of the blood and an alveolar air within normal limits.* There is no reason to suppose that acetone bodies play any significant part in the production of the acidosis occurring in the course of

29. Finkelstein and Meyer: *Jahrb. f. Kinderh.*, 1910, lxxi, 720.

30. "Die Diagnose der Intoxikation wurde erst gestellt, wenn die Symptome, die Finkelstein gefordert hat, vorhanden waren. Vor allem die Benommenheit, das Fieber und Gewichtsabfall."

31. Marriott: *Jour. Biol. Chem.*, 1914, xviii, 507.

32. Howland and Marriott: *Bull. Johns Hopkins Hosp.*, 1916, xxvii, 63.

* A discussion of the acetone bodies in the blood in ileocolitis and other conditions is reserved for a later communication.

the diarrheal conditions of the type that we have described in this paper. The acetone bodies produced may be considered to be the result of partial starvation and to have no especial relation to the underlying conditions.

It is possible that lactic acid may enter in as a factor in the production of the acidosis, but at present we have not sufficient evidence to prove or disprove this assumption. We are at present engaged in the investigation of this phase of the problem. As has been mentioned previously, Keller³³ was unable to find abnormal organic acids in the urine of infants suffering from diarrheal diseases.

Conceivably, acidosis may result from loss of base from the body, by way of the intestinal tract. Steinitz⁷ found a negative sodium and potassium balance in infants fed on high-fat diets, especially if there was a concomitant diarrhea with loss of weight, and has considered this as evidence of an alkali loss from the body. His results do not prove the point, for he failed to determine the acid constituents also lost from the body. That there should be a negative balance of all food constituents in a diarrhea with loss of weight is not to be wondered at. A negative sodium balance would occur if sodium chlorid were eliminated in excess in the stools; the relation between acid and base in the body, however, would not be altered at all. Holt, Courtney and Fales³⁴ have confirmed the results of Steinitz as to loss of sodium and potassium in diarrhea. They found however that, while sodium and potassium excretion by the bowel was greatly increased, the excretion of chlorid was increased still more! The alkali is lost from the body but acid is also lost. From the work published up to the present time no conclusions can be drawn as to whether acid or alkali predominates in the loss.

By a method devised in our laboratory, and as yet unpublished, it has been determined that in some cases with diarrheal stools there is a loss of potential acid rather than potential alkali, whereas normally there is usually a slight alkali loss. These results will be the subject of a subsequent communication.

One possibility remains as an explanation for the acidosis, namely, a failure of the acid excretory function of the kidney. Under normal conditions the kidney excretes a very considerable amount of acid, chiefly in the form of acid phosphate. A failure of this special function of the kidney would result in a retention of acid phosphate and a consequent acidosis. In severe diarrhea, the urinary secretion may be markedly diminished even to the point of complete anuria, the kidney becoming functionally more or less inactive, even though no

33. Statement by Steinitz: *Monatschr. f. Kinderh.*, 1902, i, 225.

34. Holt, Courtney and Fales: *AM. JOUR. DIS. CHILD.*, 1915, ix, 213.

organic changes may be present. That diminished acid excretion and consequent retention of acid phosphate in the body fluids would occur under these conditions would seem probable. We have a certain amount of experimental evidence in support of this hypothesis; that is to say, we have found an increase in the phosphate content of the blood serum in the course of severe diarrhea, but are not as yet prepared to say that this is surely and solely the cause of the acidosis. Further experimental work is required before this can be definitely established from the quantitative standpoint. Retention of acid phosphate, without doubt, could cause acidosis, and in the light of our present knowledge, we consider this, perhaps, the most probable explanation of the acidosis occurring with severe diarrhea.

TREATMENT

It is necessary to consider here only the treatment of the acidosis that complicates the diarrhea. To the accepted methods of treating the diarrhea itself we have at the present time nothing to add. So long as the ultimate cause of the acidosis remains obscure, we cannot employ direct measures to prevent its development. The acidosis may result, though it has not yet been proved, from loss of bases by the intestinal tract. The excessive diarrhea should be prevented, if possible, by moderate doses of opium, for, in any event, the draining of the body of water cannot be an indifferent matter. Opium in some form, such as paregoric, may be given, preferably in small doses, frequently repeated, to be reduced or stopped when the evacuations diminish in frequency or copiousness. Water must be given freely by mouth, if possible; if vomiting prevents this, as it frequently does, it must be given by rectum, subcutaneously or intravenously.

If, as has been suggested above, the acidosis is due to the retention of acid phosphates, the excretion of these substances and the consequent prevention of acidosis would be greatly facilitated by a copious secretion of urine. When acidosis develops, the secretion of urine is very scanty and often ceases for hours at a time. Under such circumstances it is most difficult to increase the activity of the kidneys. All measures should be used to prevent the cessation of the activity. The best of these is the constant administration of water or salt solution in one of the ways mentioned above.

When the presence of the acidosis is determined by the hyperpnea or by some laboratory test, energetic treatment is required. Alkalies must be administered promptly, until the reaction of the blood is again normal. We have used sodium bicarbonate for this purpose. This may be given by mouth, by rectum, subcutaneously or intravenously. Vomiting often prevents the administration by mouth, and absorption

by the bowel is unreliable in the presence of diarrhea. The soda may then be given subcutaneously or intravenously. When a sufficiently large vein can be found, intravenous administration is the method of choice, even if there is no vomiting. Immediate action can thus be obtained. The strength of the solution for intravenous use is 4 per cent. Depending on the size of the infant, from 75 to 150 c.c. should be given and repeated in three hours if the hyperpnea does not cease. A large amount of alkali is required, for not only is the alkalinity of the blood reduced but also that of all the tissues of the body. After one or two intravenous injections, the soda should be continued by mouth in doses of 1 to 3 gm. every two or three hours until the urine is alkaline to litmus. Should it be impossible to give the soda intravenously, the solution may be injected subcutaneously. There is always danger under such circumstances that necrosis of the tissues will result. The danger is minimized, if certain precautions are taken. The solution (either 2 or 4 per cent.) is sterilized by heat. By this procedure, however, a large part of the bicarbonate is transformed into the carbonate. As the carbonate is intensely irritating to the tissues, it must be transformed back into the bicarbonate. This may be done by bubbling carbon dioxide through the cold solution to which a few drops of phenolphthalein have been added until it becomes colorless.³⁵ From 100 to 300 c.c. may be employed at an injection and should be given very slowly.

The administration of soda by one or the other method will often overcome both the clinical and laboratory evidences of acidosis. We have frequently seen the hyperpnea disappear and all the tests show the reactions to be found in the normal infant. Nevertheless, the child may die—indeed, such is usually the case. The cause of death under such circumstances is not clear. It is possible that as the result of the acidosis certain processes have been initiated which render life impossible or certain others may have been inhibited without which life is impossible. It is sufficiently clear that the condition resulting from or accompanying the acidosis is most serious even if its exact nature is not understood. Therefore in all cases of severe diarrhea, even though there are no evidences of acidosis, it is advisable to use sodium bicarbonate until the urine is alkaline. Its administration may prevent the development of acidosis. When further observations have made clear the processes on which the acidosis depends, we may be able to direct our treatment more intelligently. At the present time we are forced to combat the result and not the cause.

35. Magnus-Levy: *Therap. Monatsh.*, 1913, xxvii, 838.

The following cases are cited to show that severe or even fatal diarrhea may occur without any evidence of acidosis:

CASE 1.—G. Z., 5½ months old. Strong, vigorous child at birth. Breast-fed for one month; thereafter, condensed milk, and later, modified milk. Gained weight very slowly and was poorly nourished but without definite symptoms except furunculosis. Diarrhea began suddenly on the day before admission to the hospital. Numerous large stools (twenty-four) in past twenty-four hours. No hyperpnea. Color gray. Carbon dioxid tension in alveolar air, 35 mm. Sellards' test gave deep purple color; pH, 7.75 and 8.35 after removal of carbon dioxid. Sodium bicarbonate, 3 gm. by mouth, caused an alteration in the reaction of the urine. Trace of acetone bodies in urine. Acetone bodies in blood, 30 mg. per one hundred c.c. The child died forty-eight hours after admission.

CASE 2.—A. S., 7 months old. Full-term child. Breast-fed for two months and did well. Then weaned and given milk, tea, coffee and bread. Illness began twelve days before entering hospital. Frequent loose, green stools. Temperature, 101 to 104 F. No hyperpnea. Carbon dioxid tension of alveolar air, 45.8 mm.; pH, 7.85 and 8.4 after removal of carbon dioxid. Acetone bodies in blood, 23 mg. per one hundred c.c. Died twenty-four hours after admission.

The following cases are fair examples of fatal diarrhea with acidosis:

CASE 3.—E. M., 3 months old. Vigorous child at birth. Weight, 8¾ pounds. Nursed for two months and thereafter given condensed milk in the day and nursed at night. Ill from the time of weaning. For four days before admission had vomited and refused food. Stools, frequent, large and watery. Marked hyperpnea. Carbon dioxid tension of the alveolar air, 14.3 mm.; pH, 7.2 and 7.55 after removing carbon dioxid. Hemoglobin dissociation, 17.8 per cent. at 17 mm. Acetone bodies in blood, 19 mg. per one hundred c.c. Died four hours after admission.

CASE 4.—R. S., 6 months old. Weight, 8¾ pounds at birth. Nursed for two months; thereafter given milk and water, equal parts, whenever hungry, as well as crackers and scraps from the table. Four days before admission, vomiting and diarrhea began. Stools every few minutes, yellow and watery. Temperature, 101 F., rising to 107.5 F., just before death. Marked hyperpnea. Carbon dioxid tension of alveolar air, 25 mm.; pH, 7.3 and 7.9 after removing carbon dioxid. Sellards' test, positive (no color). Acetone bodies, 21 mg. per one hundred c.c. Died twenty hours after admission. Necropsy findings negative except for slight congestion of mucous membrane of colon.

CASE 5.—T. B., 6 months old. A small child at birth. Nursed for two months, then weaned and given a mixture of milk, water and sugar. Weight at 6 months, 12 pounds. Onset, acute, twenty-four hours before admission to the hospital. There was vomiting after every feeding and a profuse, watery diarrhea. Ten stools in twenty-four hours. Child much prostrated. Hyperpnea marked. Carbon dioxid tension of alveolar air, 21 mm.; pH, 7.25 and 7.45 after removing carbon dioxid. Hemoglobin dissociation, 13 per cent. saturation at 17 mm. Acetone bodies in blood, 22 mg. per one hundred c.c. Death occurred eight hours after admission. Necropsy showed slight ulceration in the ileum and colon, hyperplastic mesenteric lymph nodes and a fatty liver.

CASE 6.—A. A., 7 months old. Nursed for two months; thereafter given condensed milk. For two weeks had had frequent loose green stools, containing mucus. Admitted to the hospital in a wretched condition. Weight, 9.5 pounds. Hyperpnea not present. Carbon dioxid tension of alveolar air, 30 mm.; pH, 7.75 and 8.15 after removing carbon dioxid. Sellards' test nega-

tive. Sodium bicarbonate, 4.5 gm., given by mouth, causing a rise of the carbon dioxid tension of the alveolar air to 35 mm. After 12 gm. of soda, the urine became alkaline.

The child did well for four days, but at the end of this time, developed a pneumonia which was quickly fatal. The acidosis in this case was mild and was readily overcome. It was not sufficient to cause so marked an increase of pulmonary ventilation as to be recognized as hyperpnea, nor was the reduction of the alkali of the blood sufficient to cause a positive Sellards' test. The low carbon dioxid of the alveolar air and the increased hydrogen ion concentration of the blood serum showed unmistakably that acidosis was present.

SUMMARY

Acidosis is found in many cases of severe diarrhea not of the ileocolitis type. The clinical expression of the acidosis is hyperpnea.

The presence of the acidosis has been confirmed by determining a lowering of the carbon dioxid tension of the alveolar air, by an increase in the hydrogen ion concentration of the blood serum, by a diminution of the alkali reserve of the serum, by an increase in the amount of alkali required to alter the reaction of the urine (alkali tolerance) and by a diminution of the combining power of the hemoglobin with oxygen.

It has been shown that the administration of sodium bicarbonate will often bring about a cessation of the hyperpnea and cause the laboratory tests to give the results that are found with normal infants.

The acidosis is not due to the presence of acetone bodies. It has not been demonstrated that it is due to loss of base. It is probable that it is due to deficient excretion of acid phosphate by the kidneys.

Johns Hopkins Hospital.

STUDIES IN THE METABOLISM OF CHILDREN

1. THE EXCRETION OF CREATININ AND OF CREATIN IN ACUTE NEPHRITIS *

IRVING S. CUTTER, M.D., AND MAX MORSE, Ph.D.
OMAHA.

It is to be expected that the excretion of creatin and of creatinin during acute nephritis in the child will show variations from the normal and from the adult normal; for it has been known for several years, through the earlier work of Amberg and Morrill¹ and the later investigations of Rose, of Folin, and of Sedgwick, that creatin, an unusual component in the adult, is a normal constituent of children's urine and that the relation between relative muscle mass and creatinin output, which holds for the human organism at and beyond puberty⁵ breaks down in children at earlier ages. Again, many investigations demonstrate nitrogen retention in cases of nephritis, experimental and pathologic.⁶ As far as we are aware, however, it has not been determined what occurs in the child under such conditions. There are a few isolated reports⁷ bearing on the point but they are not of a character to assist us in a rationale of child metabolism with respect to the components with which this paper is concerned. Very valuable determinations of the creatin and creatinin content of the blood of nephritic subjects have been made on adults,⁸ indicating the character of retention.

In the present paper, we present the data derived from a study of two children⁹ aged 5 and 13, whose cases were followed for periods of

* Submitted for publication Feb. 17, 1916.

* From the Biochemical Laboratory of the University of Nebraska College of Medicine, Omaha.

1. Amberg and Morrill: Jour. Biol. Chem., 1907, iii, 311.

2. Rose, W. C.: Jour. Biol. Chem., 1911, x, 265.

3. Folin, O.: Jour. Biol. Chem., 1912, xi, 253.

4. Sedgwick, J. P. R.: Tr. of the Section of Diseases of Children, A.M.A., 1910, p. 105.

5. Folin, O.: Am. Jour. Physiol., 1905, xiii, 66. Van Hoogenhuyze and Verploegh: Ztschr. f. physiol. Chem., 1905, xlvi, 415.

6. Mosenthal, H. O.: Arch. Int. Med., 1904, xiv, 844; Proc. Soc. Exp. Biol. and Med., 1915, xiii, 9. Folin and Denis: Jour. Biol. Chem., 1914, xvii, 487. Davis and Foster: Proc. Soc. Exper. Biol. and Med., 1915, xiii, 33. Older literature in Roseman, R.: Arch. f. d. ges. Physiol., 1898, lxxii, 467.

7. E. g., Mohr, L.: Ztschr. f. klin. Med., 1903-4, li, 331.

8. Folin and Denis: Jour. Biol. Chem. 1914, xvii, 487.

9. We express our obligations to Dr. B. W. Christie, physician to the Clarkson Hospital, Omaha, for the opportunity to study these cases.

thirty-five days and ten days, respectively. The former, a boy, H. J., was under the care of a special nurse, the latter, likewise a boy, R. Mc., was attended by the floor nurses. In both cases, especial care was given to the collection of the daily twenty-four hour specimens of urine. The diets in each case were practically creatin and creatinin-free, being administered for minimum protein maintenance, calculated in calories.¹⁰ In the case of R. Mc., the temperature (Fig. 1) was practically normal except at the beginning of the disease. Inasmuch as pyrexial conditions of whatever origin have been shown to modify the tolerance for creatinin and for creatin,¹¹ it is important to have these data in hand. In the other case, H. J., the temperature chart was not available.

The urines were deproteinized by the use of colloidal iron. The creatinin determinations were made according to the usual Folin method, the creatin by difference according to the modification by S. R. Benedict¹² of Folin's original method.



Fig. 1.—Temperature Chart for Case of R. Mc.

The most conspicuous feature of the curves of excretion of both constituents and in both cases is the wide variation from day to day. Moreover, this variation, which approaches a rhythm, is independent of all known concomitant factors, such as food, temperature, etc. It appears that a threshold exists which, on being reached, leads to excretion of the creatin and creatinin. Retention in the sense of almost if not quite total suppression of excretion of these components does not exist for a period of more than twenty-four hours. In fact, there is a *negative* balance in every instance in which a period of one week

10. A typical diet for both cases is that of November 18: Breakfast, 6:30 a. m., cereal (cooked) 2 tablespoonfuls, cream, $\frac{1}{4}$ pint; 9:30, milk, 8 oz. Lunch, 12 m., bread, 1 slice, butter (50 cal.), potato (1 baked). Dinner, 5:30 p. m., cereal (as at 6:30 a. m.), bread (as at noon), butter (as at noon), cream (as at 6:30).

11. Leathes, J. B.: Jour. Physiol., 1906-7, xxxv, 205. Shaffer, P. A.: Am. Jour. Physiol., 1908, xxiii, 1, p. 13.

12. Benedict, S. R.: Jour. Biol. Chem., 1914, xviii, 191.

or over is considered. We have here then, apparently, a condition which varies markedly from that which has been reported for the adult, in whom retention of creatin and creatinin is described.¹³

The curves exhibit no correlation between the behavior of creatinin and that of creatin. It is impossible to determine anything which might suggest an origin of one from the other.

For comparison with normal children, a study of creatin and creatinin excretion in several boys and girls of ages varying from 9 months to 12 years was made.¹⁴ The results obtained are given in Table 1.

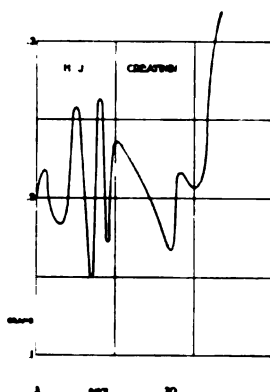


Fig. 2.—Curve 2: creatinin elimination in "H. J."

TABLE 1.—CREATIN AND CREATININ EXCRETION IN CHILDREN

Case	Age (yrs.)	Creatin in 24 hours.	Creatinin in 24 hours.
A.....	5	0.00*	0.312
B.....	3	0.040	0.130
C.....	3	0.00*	0.348
D.....	3	0.010	0.251
E.....	3	0.135	0.130
F.....	4	0.00*	0.310
G.....	$\frac{3}{4}$	0.274	0.245
H.....	3	0.089	0.323
I.....	11	0.570	0.870
J.....	1	0.070	0.059
K.....	12	0.510	0.760
L.....	8	0.110	0.550

* Not determined.

Judging from these figures, the averages for the two cases of nephritis are somewhat low. This is not to be interpreted without

13. Lampert, D.: Ztschr. f. klin. Med., 1914, lxxx, 498, where a review of the subject may be had.

14. The writers cannot express too warmly their appreciation for the painstaking care with which these samples were furnished us by Miss René MacKenzie, R.N., of the Child Saving Institution, Omaha.

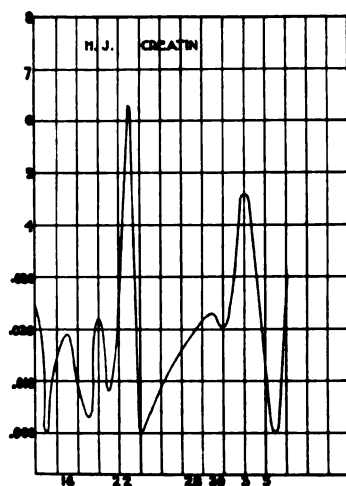


Fig. 3.—Curve 3: creatin elimination in "H. J."

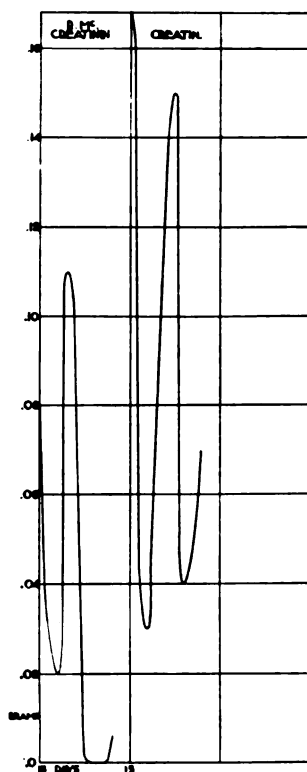


Fig. 4.—Creatinin (to 15), creatin (part 15), for "R. Mc."

analysis as retention, for in the cases of nephritis we are dealing with the child at rest. Moreover, this immobility is in itself a condition which approaches the abnormal, or pathologic. While we are aware that exercise does not apparently affect the output of creatinin or of creatin in the adult, yet in children inactivity in itself is conducive to a loss of tone and sometimes of weight. Hence we must not assume, until more figures are obtained from further study, that the lower output of these children means retention in the sense in which biochemists speak of nitrogen retention.

It is desirable to mention one difficulty in the study of creatin and creatinin metabolism in very young children and in children in whom there is a retention of these components even during a twenty-four hour period, namely that of reading the colorimeter when small amounts of creatinin are present. Our results were obtained by the dilution method, that is, by diluting the urine according to the amount of creatinin present. Amberg and Morrill and others have concentrated the urines, but this seems to us to be precarious. Therefore, though the figures that we give must have an element of error in them, the error is constant and inasmuch as we desire relative data, the results are adequate. Inasmuch as there was, throughout, no sugar present, no attention was given to the possible modification of the creatin fraction. From the observations of Wolf and Osterberg¹⁶ and others, unless acetonuria and glucosuria are pronounced, the creatin fraction is not materially modified.

CONCLUSIONS

1. Retention of creatinin and of creatin nitrogen in the cases of nephritis in children presented here is a matter of less than twenty-four hours.
2. The excretion of these components varies widely from day to day and their amounts are not correlative with pyrexial, nor with other known conditions.
3. No other quantitative study similar to the present one has been made as far as we are aware.
4. There is a wide divergence between the data reported for adults and those determined by us for children.

Forty-Second and Dewey Avenues.

16. Wolf, C. G. L. and Osterberg, L.: *Am. Jour. Physiol.*, 1911, xxviii, 71, Cathcart and Orr: *Jour. Physiol.*, 1914, xlviii, p. xxi.

STUDIES IN THE METABOLISM OF CHILDREN

II. CREATIN RETENTION IN MARASMUS *

IRVING S. CUTTER, M.D., AND MAX MORSE, Ph.D.

OMAHA

The fact seems established, through the investigations of many workers,¹ that in the adult, fasting involves an increase in the excretion of creatin. As far as we are aware, this condition has not been identified in the young. Fasting, however, affects the creatin output differently in different species of animals, for while in the adult of the human species, an increase in this component is observed, the reverse is the case in starving dogs.² McCollum and Steenbock³ find the pig refractory under the influence of starvation.

Mellanby⁴ reported a case of cyclic vomiting (recurrent vomiting) in a boy of 6 in which marked loss in weight occurred during the attacks. He speaks of creatin excretion in a child of 6 as being an abnormality and says also that there was an increase in creatin excretion two and three days *before* the attack, during which and after which loss in weight occurred. It is not possible to draw satisfactory conclusions from this paper.

In a similar investigation, Sedgwick⁵ reports abnormal creatin excretion (an augmentation) during attacks of recurrent vomiting in several cases of children from 2 to 10 years of age. The data exhibit no correlations with loss in weight, but the rise in creatin runs *pari passu* with the appearance of febrile conditions.

In the case which we present herewith, there is a clear *lowering of creatin excretion during a long period of loss in body weight*. The weight curve is given in the chart. Vomiting occurred after each intake of food *per os*, due, apparently, to pyloric spasm⁶ and this condition did not cease entirely after the growth curve began to rise, following the use of mother's milk (Oct. 16, 1915). Creatin deter-

* Submitted for publication Feb. 17, 1916.

* From the Biochemical Laboratory of the University of Nebraska College of Medicine, Omaha.

1. Van Hoogenhuyze and Verploegh: Ztschr. f. physiol. Chem., 1905, xlvi, 415.

2. Howe, Mattill and Hawk: Jour. Biol. Chem., 1912, xi, 103.

3. McCollum and Steenbock: Jour. Biol. Chem., 1912, xiii, 209.

4. Mellanby, E.: Lancet, London, 1911, ii, 8.

5. Sedgwick, J. P.: AM. JOUR. DIS. CHILD., 1912, iii, 209.

6. This diagnosis was made by the attending physician, Dr. Clyde Moore, whose interest in the case and whose kindness made it possible to study it carefully. To Miss René MacKenzie of the Child Saving Institute we are especially indebted.

minations were made by the Folin method and by Benedict's modification, practically identical results being given in the two cases. The creatinin excretion apparently was normal for a child of that age (2) and rose gradually, as in the normal child, regardless of the growth curve. All data refer to twenty-four hour amounts, the samples being taken by a modification of the method of Schabad.⁷

CREATININ AND CREATIN EXCRETION IN A CASE OF MARASMUS

Date	Creatinin Gm.	Creatin Gm.
10/ 2/15.....	0.144	0
10/13/15.....	0.144	0
10/15/15.....	0.195	0
10/19/15.....	0.201	0
10/25/15.....	0.212	0.028
10/29/15.....	0.218	0.050
11/ 8/15.....	0.295	0.072

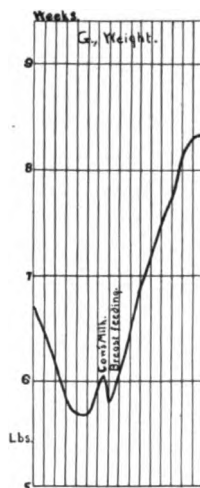


Chart of weight curve in case of marasmus.

CONCLUSION

In the case of a male child of 2 years, whose curve of growth gradually fell on account of pyloric spasms, the creatin excretion remained practically suppressed until the growth curve began to rise consequent on breast feeding. Creatinin excretion remained normal during the whole period.

Forty-Second and Dewey Avenues.

7. Schabad, J. A.: Arch. f. Kinderheilk., 1908, xlviii, 402.

TWO CASES OF OBSTETRICAL PARALYSIS INVOLVING ONLY THE MUSCULOSPIRAL NERVE *

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With the exception of facial nerve palsies, paralysis of a single peripheral nerve present at the time of birth is a rare condition. Clear descriptions of musculospiral paralysis of the newly born cannot be found in the literature. The two cases here reported came under observation in the outpatient department of the Harriet Lane Home of the Johns Hopkins Hospital.

REPORT OF CASES

CASE 1.—Oct. 3, 1914, B. B., a girl, 19 days old, was brought to the dispensary by her mother because she did not move her left hand.

Family History.—Father 28 years old; mother 25 years old; both healthy; two children in addition to the patient, 3 years old and 9 months old, respectively; both normal; no history of miscarriage or stillbirths, or of lues.

Past History.—The patient was born spontaneously, at term, after a precipitate labor. The mother had been having pains throughout the day of September 14, and in the evening called in the midwife who had attended her at the birth of the two other children. The midwife found the mother up and about, getting supper. Three hours later the midwife was hurriedly summoned and before there was any time to assist, the baby "popped out into the bed," as the midwife described it. One loose coil of cord about the neck was easily removed. Slight cyanosis was present. The baby is said to have weighed 8 pounds.

Following birth, the baby had no convulsions or sickness of any kind, nursed well and was not cyanosed; no evidence of congenital lues. Nothing abnormal about her was noted except the local condition in the left arm presently to be described.

Eight days after birth the mother first noticed that the baby did not move the left hand as she did the right. The left hand looked to her deformed, but did not seem to be in any way painful.

Physical Examination.—A well-nourished baby, 19 days old, weighing 8 pounds, 10 ounces; temperature normal; head, well formed; anterior fontanel normal in size and tension; pupils equal and react to light; extra-ocular movements normal; no ptosis; eardrums normal; no facial paralysis; superficial lymph nodes not enlarged; thorax normally shaped; heart normal; lungs clear; contour of abdomen normal; liver edge felt just below costal margin; spleen not felt; genitalia normal; the legs and the right arm are moved by the child freely, in all directions, in an entirely normal manner.

The left upper arm is kept in very much the same position as the right upper arm, but the left forearm is held flexed at the elbow, so that it forms a right angle with the upper arm, and the hand is held in the typical position of wrist-drop. The upper arm can be moved in all directions by the child, exactly like

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* From the Harriet Lane Home and Department of Pediatrics, Johns Hopkins University.

the right, but although the child can flex the forearm when it is passively extended, there is never any attempt at extension of the forearm against gravity; in fact, when the forearm is extended passively, there is an immediate return to the position of flexion. The fingers can be extended slightly when they are flexed, but there is no limitation of flexion. The wrist-drop remains constantly present, unless the hand is passively brought into a position of extension or falls into a position of extension from gravity, but as soon as the forearm is held upright, and the support of the hand in the position of extension released, the hand tumbles back into the position of wrist-drop. There is no hindrance to passive motion either in the muscles or joints, nor does passive motion seem to be painful. No bony deformity can be felt anywhere. The contour of the humerus, as felt through the soft parts, is entirely normal. On examination of the different muscles, so far as it is possible to do this accurately in so young a child, it is found that the deltoid, biceps and flexors of the wrist and fingers act normally, while the triceps, supinators and extensors of the wrist, and to a less degree, the extensors of the fingers, have no power at all. The paralysis is, then, limited to the distribution of the musculospiral nerve.

The Roentgen-ray examination shows a normal condition. The Wassermann is negative.

Oct. 15, 1914: (Baby 31 days old). Electrical examination by Dr. Taneyhill shows reaction of degeneration (galvanic stimulation) in triceps, extensor muscles of the wrist and supinator longus; reaction of deltoid normal.

Oct. 22, 1914: The condition of the left arm remains the same; electrical reactions, which are repeated, unchanged.

Nov. 5, 1914: Some movement in the triceps is noted; reaction of degeneration plainly visible in anconeus; still present in extensors of wrist and supinator longus.

Dec. 10, 1914: Noticeable improvement; only feeble reaction of degeneration in triceps and extensors of wrist.

Feb. 18, 1915: The left arm is entirely normal. The pathologic condition has disappeared without leaving a trace of its existence.

CASE 2.—May 13, 1915, O.T., a girl, 13 days old, was brought to the Harriet Lane Dispensary by her mother from the obstetrical department of the Johns Hopkins Hospital, for routine examination previous to discharge.

Family History.—Father, 24 years old; mother, 19 years old; both healthy; no other children, but the mother had a miscarriage at the second month, nine months previous to the birth of the patient; no history of lues.

Birth History.—The baby was born spontaneously, at term, after long, difficult labor; mother's pelvis funnel shaped. Presentation, L.O.A.; first stage 59 hours, 14 minutes; second stage 1 hour 24 minutes; third stage 8 minutes, making a total of 60 hours, 46 minutes; mother was given narcophin 0.5 gm. and scopolamin 0.045 gm.; one injection of narcophin and scopolamin and four injections of scopolamin alone were given. The first dose was administered 6 hours and 46 minutes before delivery, with the cervix 6 cm. in diameter; pains every four minutes. Chloroform was given at end of labor, 10 c.c. for 20 minutes; 1 c.c. of pituitary fluid was given during second stage; mother very restless and restrained with difficulty; child apneic; hot and cold tubs given for 30 minutes; artificial respiration necessary; heart action good from the first.

Past History.—Immediately after birth it was noted in the obstetrical department that marked asymmetry of the face and chest existed. The right side of the face and thorax were flattened and pushed inward as if considerable pressure had been present during labor. This asymmetry disappeared by the second day. It was also noted, immediately after birth, that the left hand was held flexed on the forearm and that the hand was in the typical wrist-drop position, and also that on the outer surface of the left upper arm, a short distance above the external condyle, a small, reddish tumor-like swelling was present. The birth weight was

5 pounds, 15 ounces. The baby had no fever or convulsions and did not develop any symptoms suggestive in any respect of lues. She nursed normally every three hours. The stools were normal.

Physical Examination.—May 13, 1915: Thirteen day old baby, weighing 5 pounds, 5 ounces; head normally shaped; anterior fontanel normal in size and of normal tension; pupils, equal and react to light; no strabismus or ptosis; ear drums normal; no facial paralysis; no enlargement of superficial lymph nodes; thorax, well formed, without showing any evidence of the asymmetry which was noted immediately after birth; heart normal; lungs clear; liver edge felt at level of umbilicus, in right mammillary line; spleen not felt; both legs and the right arm are moved by the child freely in all directions and show no abnormality.

The left arm is held semiflexed at the elbow and the hand is flexed on the forearm in a position of wrist-drop. On stimulating active motion, it is found that the child can move the arm in a normal manner at both the shoulder and elbow joints, and extend the forearm against gravity. The child, too, can slightly supinate the hand but cannot be made to extend the fingers, which are held in a flexed position. After the fingers and wrist are extended passively, they immediately drop back into their former position. No sign of pain can be elicited by palpation and no bony deformity can be found in any of the bones of the forearm, or about the shoulder girdle on the left side. The deltoid, triceps, biceps and flexors of the wrist and fingers have normal power. The supinators and extensors of the wrist and fingers seem, however, to be paralyzed. The paralysis in this case also appears limited to the distribution of the musculospiral nerve.

On the outer surface of the upper arm about 2 cm. above the external condyle is an oval, red, elevated area, situated with its long axis in the long dimension of the arm. It is about 3 cm. long and 1.5 cm. wide. It seems to lie chiefly in the deep tissues and to involve the skin, but to be freely movable on the bone below, though it is not absolutely certain that it may not be connected with the bone by a pedicle. The center of the tumor is softer than the periphery and fluctuates, while the rather broad border surrounding the fluctuating area is indurated and firm. Palpation of the area does not seem to be painful, though it is not positively certain that no pain is present. Aspiration of the mass results in withdrawal of a few drops of a thick, yellowish-white material, which, when stained and examined with the microscope shows only a cellular detritus with some disintegrating, swollen cells, thought probably to have been pus cells, but no organisms of any kind. On the following day the mass was again aspirated and a few drops of bloody fluid were obtained, apparently chiefly composed of fresh blood. No organisms were seen in the smears from this fluid, and cultures planted on agar mediums were sterile.

May 20, 1915: The mass is distinctly smaller, measuring now 2 by 1 cm.; no fluctuation can be obtained, but the central part of the mass feels distinctly depressed, as if a loss of substance had taken place in its central part. The character and extent of the paralysis are exactly the same as at the first examination. Electrical examination by Dr. Taneyhill shows reaction of degeneration of the supinator longus and extensors of the wrist; biceps, triceps and deltoid, normal.

June 12, 1915: (Baby 43 days old). The skin is only very slightly indurated over the site of the mass on the outer side of the arm and there is no evidence of any paralysis whatsoever. The child moves the left hand and fingers exactly as the right.

DISCUSSION

The commonest form of obstetric paralysis is the well-known upper arm or Duchenne-Erb type, first accurately described by Duchenne,¹ but often called Erb's paralysis; incorrectly, however, since Erb's description was of a similar condition in the adult produced by injury to the fifth and sixth cervical roots.²

Next in frequency is the rather rare form of obstetric paralysis known as the lower arm or Klumpke³ type, which is concerned with the disturbance of the lower roots of the brachial plexus, the seventh and eighth cervical and first dorsal roots, and gives rise to symptoms chiefly in the distribution of the ulnar and median nerves. Since the ramus communicans between the eighth cervical and the first dorsal and sympathetic is also injured, certain eye signs, such as narrow lid slit and contracted pupil on the same side as the lesion, may be present and aid in the localization of the injury.

The third form of birth palsy is in reality merely a combination of the two forms just described, and may be of such severity as to give rise to a complete paralysis of the arm.

The pathogenesis of these forms of obstetric paralysis is not absolutely certain. It seems most likely that the upper arm type is produced by stretching of the roots of the brachial plexus, while there may be actual rupture of the nerve trunks in severe cases. Theoretically any manipulation which tends to widen the angle formed by the neck and shoulder in delivery should tend at the same time to stretch the roots of the brachial plexus on that side, if severe enough, with injury even to the point of rupture. It is not so easy to explain the pathogenesis of the lower arm type of obstetric paralysis, but the series of cases collected from the literature by J. J. Thomas⁴ indicates that the majority are connected with breech delivery.

Other causes have been advanced to explain injury to the brachial plexus in obstetric paralysis, such as fracture or separation of the upper epiphysis of the humerus, dislocation of the shoulder or fracture of the clavicle. But when present, these pathologic conditions of the bones or joints attest rather to the severity of the strain to which the parts were subjected than to a specific injury to the plexus by the fracture or dislocated bone itself.

1. Duchenne: *Paralysies obstétricales infantiles du membre supérieur, sans complications. De l'électrisation*, Ed. 3, 1872, p. 537.

2. Erb: *Handbuch der Elektrotherapie*, Ed. 2, 1886, p. 305.

3. Klumpke: *Paralysies radiculaires du plexus brachial*, *Rev. d. méd.*, 1885, v, 591.

4. Thomas, J. J.: *Two cases of Bilateral Birth Paralysis of the Lower Arm Type*, *Boston Med. and Surg. Jour.*, 1905, cliii, 431.

Injury to a single peripheral nerve may occur (1) before, (2) during or (3) after labor. The single nerve most commonly injured is the facial, and the injury is due usually to direct pressure of the forceps on the nerve itself.

Prenatal cases of paralysis of the musculospiral nerve, due to the pressure of amniotic bands about the arm, have been reported by Bonnaire,⁵ Spieler,⁶ Cassirer⁷ and Ballantyne⁸ and reference to this condition is made by Cautley⁹ in his textbook, and also by Zappert¹⁰ in his discussion of obstetric paralysis in Pflaundler and Schlossman's work. In each of the cases reported, pressure marks of the constricting band were visible on the arm, showing the site of the lesion and also its causation.

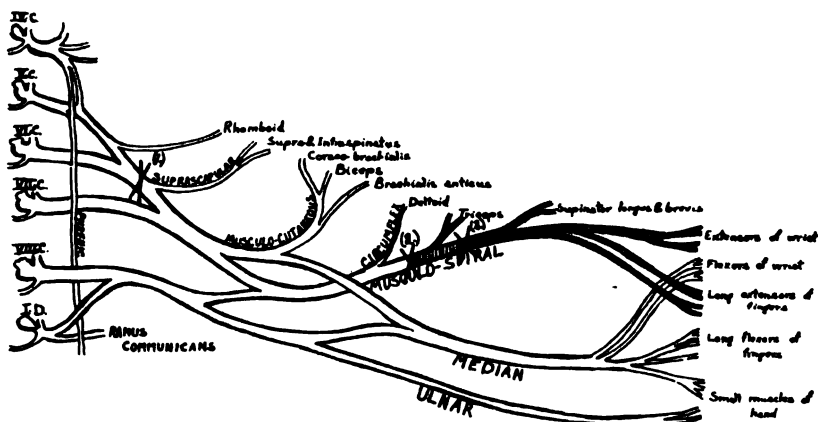


Diagram of Brachial Plexus.—1. Region of "Erb's Point." 2. Case 1: The site of the lesion in the musculospiral nerve is between its branch to the deltoid (circumflex) and its branches to the triceps. 3. Case 2: The site of the lesion is distal to the muscular branches to the triceps but proximal to the branches given off to the supinator muscles.

Injury to the musculospiral nerve at the time of birth may be secondary to bone injury, particularly of injury to the humerus, as is readily understood when the close anatomic relationship that exists between the musculospiral nerve and the humerus is considered. T. T.

5. Bonnaire: (Case) *Centralbl. f. Gynäk.*, 1898, xxii, 914.

6. Spieler: *Einen Fall von traumatischen Radialislähmung*, *Jahrb. f. Psychiat.*, 1903, xxiii, 415.

7. Cassirer: *Ueber Schädigung Nerven durch intrauterin entsandene Schnurfurchen*, *Deutsch. med. Wchnschr.*, 1905, xxxi, 1221.

8. Ballantyne: *Antenatal Pathology and Hygiene*, p. 186.

9. Cautley: *Diseases of Infants and Children*, 1910.

10. Zappert: *Organic Diseases of the Nervous System*, Pflaundler and Schlossmann, 1908, iv, 262.

Thomas¹¹ reports a case of musculospiral paralysis shown by the presence of wrist-drop associated with dislocation of the head of the humerus, with improvement after the dislocation was released. Kramer¹² and Gangolphe¹³ have reported musculospiral paralysis in connection with the fracture of the humerus, and Bernhardt¹⁴ gives a fracture of the bones of the lower arm as a possible cause.

Injury to the peripheral nerves after birth is exceedingly rare in infants and young children. "Children do not appear to be very liable to injury of the nerves in spite of the many accidents which befall them. I have not seen a case of traumatic neuritis in the plexus of a child below the age of 14 years excepting the form of brachial neuritis just described" [obstetrical paralysis].—(Starr.)¹⁵ Gowers¹⁶ mentions the fact that musculospiral paralysis is not uncommonly found in Russian infants as a result of a popular practice of binding the arms to the body and then laying the child on its side. Bernhardt,¹⁴ Hirt¹⁷ and Gibson-Fleming¹⁸ also give this as a cause.

Burr¹⁹ reports a number of obstetric paralyses in which he assigns the lesion to the motor cells of the cord, conceiving of the condition as an unusual manifestation of poliomyelitis.

Instances of musculospiral paralysis due to birth injury appear in the literature, but no accurate descriptions of them have been given. Ott²⁰ says relative to this condition, "When the nerve is injured high up, the triceps muscle is paralyzed. Then you may have as in one case of mine *where the nerve was injured during the birth of the child*, loss of power to extend the forearm and of supination of the hand." Haslinger²¹ reports a case in which a paresis of the left facial nerve was noted immediately after birth and five days later peripheral paralysis in the distribution of the right musculospiral nerve. The tri-

11. Thomas, T. T.: Laceration of the Axillary Portion of the Capsule of the Shoulder Joint as a Factor in the Etiology of Traumatic Combined Paralysis of the Upper Extremity, *Ann. Surg.*, 1911, liii, 77.

12. Kramer: *Nervenverletzungen*, Lewandowsky's *Handbuch der Neurologie*, ii.

13. Gangolphe: *Paralysie radriculaire traumatique du plexus brachial*, *Lyon méd.*, 1906, cvii, 977.

14. Bernhardt: *Die Erkrankungen der peripherischer Nerven*, Nothnagel's *Handbuch*, 1895, xi.

15. Starr: *Nervous Diseases, Organic and Functional*, 1913, p. 179.

16. Gowers: *Diseases of the Nervous System*, Ed. 2, 1892, i, 85.

17. Hirt: *Musculo Spiral Paralysis, Diseases of the Nervous System*, 1899.

18. Gibson-Fleming: *Diseases of Spinal Nerves*, Allbutt and Rolleston's *System of Medicine*, 1911, vii.

19. Burr: *Spinal Birth Palsies; A Study of Nine Cases of Obstetrical Paralysis*, *Boston Med. and Surg. Jour.*, 1892, cxxvii, 235.

20. Ott: *Clinical Aspect of Some Peripheral Palsies*, *Philadelphia Med. Times*, 1884, xv, 268.

21. Haslinger: (Reference), *Centralbl. f. Gynäk.*, 1899, xxiii, 1173.

ceps in Haslinger's case remained normal. Fairbank²² states that a wrist-drop may be a residual paralysis of a more extensive birth palsy, the bulk of which has been entirely recovered from. Zappert¹⁰ makes mention of a case in which musculospiral paralysis was the result of intrapartum pressure on the nerve, but does not describe it in further detail. Oppenheim²³ makes the statement, "It is not common for obstetric paralysis to be limited to this nerve (musculospiral) or to affect it chiefly, though I have observed this."

The distribution of the paralyses in these two cases is limited to the muscles supplied by the musculospiral nerve. *No muscle not supplied by the musculospiral nerve was affected.* In Case 1 the supinators and extensors of the wrist and the triceps were paralyzed; in Case 2 only the supinators and extensors of the wrist.

The fibers of the sixth, seventh and eighth cervical roots pass not only into the musculospiral nerve, but also into the nerves supplying the deltoid, biceps and flexors of the wrist, so that these latter muscles are affected in addition to those supplied by the musculospiral nerve when the injury lies in the sixth, seventh and eighth cervical roots. Since the deltoid, biceps and flexors of the wrist were unaffected in the two cases under discussion, the lesion cannot lie in the cervical roots, but must lie peripheral to them, in the musculospiral nerve itself. The site of the lesion in the musculospiral nerve must lie, in Case 1, between its branch to the deltoid (the circumflex), which was not paralyzed, and its branches to the triceps, which were paralyzed. The lesion in Case 2 must lie lower down, distal to the muscular branches to the triceps, but proximal to the branches given off to the supinator muscles, since the triceps remained intact while the supinators were affected.

If the causes of peripheral palsies affecting the upper extremities of infants are considered, it is possible to exclude the majority of them without difficulty as being operative in these two cases. It is possible to exclude antenatal injury in its only well-recognized form, namely, pressure from amniotic bands, as a causative factor. The surface of the arm was entirely normal in Case 1, and the mass described on the outer side of the arm in Case 2 might, perhaps, when first seen, have been considered of inflammatory nature or as a new growth, but not, by any possibility, as the pressure mark of a constricting band. It is possible, also, to exclude in both cases traumatism from a dislocated or fractured bone, as neither of these conditions was present. Nor is it possible to think that the musculospiral nerve was injured after birth in these two patients, for their arms were not

22. Fairbank: A Lecture on Birth Palsy; Subluxation of the Shoulder Joint in Infants and Young Children, *Lancet*, London, 1913, i, 1217.

23. Oppenheim: *Lehrbuch d. Nervenkrankheiten*, Ed. 2, 1898, p. 320.

bound to the body, nor did either infant receive any injury or trauma. It is scarcely necessary to consider poliomyelitis as a possible cause when it is remembered that the paralysis in one case was noted immediately after birth, and that in the other case the baby had had no fever or shown any sign of acute illness. Moreover, the limitation of the paralysis to a peripheral distribution in both cases is most difficult to explain on the basis of motor cell injury in the anterior horn. The paralysis cannot be regarded as the residual of a birth paralysis which was originally more extensive. The muscles, other than those described as being paralyzed, were entirely normal in both cases a few days after birth, as was determined by careful examination. The paralyzes in obstetric palsies do not disappear as rapidly as this. Restitution to the normal, if it occurs at all, is a matter of weeks or months rather than of days. Moreover, if the paralysis had been originally more extensive, the lesion must have been higher up in the plexus in the fifth and sixth cervical roots. If this had been the case, why should the fibers in the roots passing to the musculospiral nerve be the only ones severely affected, while those passing into the circumflex and musculocutaneous remained essentially unaffected?

It is impossible to determine exactly what was the manner of production of the paralysis in Case 1, but it seems almost certain that the injury must have occurred during the birth of the child. It is a very common experience, particularly in dispensary practice, to find that extensive obstetric paralysis is not noticed for a considerable period after birth, and when it is suddenly brought to the attention of those about the child, the inference is made that it has been recently acquired. It is practically certain in Case 2 that the injury to the musculospiral nerve was acquired during birth. It is established that the mother had a funnel-shaped pelvis and that the labor was long and difficult; in other words, that the conditions for pressure injury in the child were present, and that the child immediately after birth showed evidences, in the asymmetry of the face and chest on the opposite side to the lesion in the arm, that she had been subjected to extreme degrees of pressure.

It is exceedingly interesting that the mass which was described as situated on the outer surface of the arm about 2 cm. above the external condyle should exactly overlie the musculospiral nerve at the calculated point of injury. It is impossible to say exactly what this mass was. Apparently it was not inflammatory, because the smear from it showed no organism and it was sterile on subsequent culture. Moreover, it spontaneously disappeared, so that it cannot be explained on the basis of tumor. It seems probable, particularly from its subsequent behavior, that the mass was a hematoma, although it is difficult to understand how the child acquired a hematoma in

this particular place. There is no evidence that the arm could have been caught in any way against the pelvis, as might have been the case, for example, if the arm had presented extending downward between the pelvis and the head. In any event, it seems highly probable that the mass and the paralysis in Case 2 were associated, since the mass exactly overlay the point at which the nerve must have been injured. Both were probably the result of a common pressure exerted during passage of the child through the pelvis. Complete healing took place in both cases in an exceedingly short time, a fact which indicates that the injury to the nerve was relatively mild, and in the nature of a contusion rather than a laceration.

The following additional references may be consulted:

Clark, Taylor and Prout: A Study on Brachial Birth Palsy, *Am. Jour. Med. Sc.*, 1905, cxxx, 670.

Thomas, H. M.: Obstetrical Paralysis, Infantile and Maternal, *Bull. Johns Hopkins Hosp.*, 1900, p. 279.

THE PERMEABILITY OF THE GASTRO-ENTERIC TRACT OF INFANTS TO UNDIGESTED PROTEIN*

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I. INTRODUCTION

The possible absorption of unaltered or incompletely digested protein is a question of more than academic interest. It is well established that the introduction of foreign protein into the circulation may provoke certain specific reactions (formation of precipitins, sensitization, etc.). Nutritional disturbances in infants fed on cow's milk have been attributed to the biologic character of the food. According to our present conceptions the specific biologic properties of animal tissues reside in great part, if not entirely, in the protein constituents. It is generally believed, however, that the proteins are split into amino-acids before absorption. If such is universally true, biologic reactions to cow's milk would be unlikely, as it has been demonstrated that specificity is lost in protein cleavage products lower than the peptones.

Ganghofer and Langer¹ found that the intestinal tract of young animals permitted the passage of heterologous protein (beef, egg) as determined by precipitin tests applied to the blood serum. When physiologic quantities were given, this occurred only in animals less than eight days old. After this time the tests were not positive, except with massive doses of the foreign protein or when the intestinal tract was subjected to chemical injury. In two debilitated infants, absorption of undigested egg protein was demonstrated by precipitin tests applied to the blood.

Mayerhofer and Pribam² observed that in acute enteritis there was an increased permeability of the intestinal wall to both crystalloids and colloids. Hamburger and Sperk³ could not demonstrate absorption of foreign protein when small quantities were fed, nor did they find

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1. Ganghofer and Langer: Ueber die Resorption genuiner Eiweisskörper im Magendarmkanal neugeborener Tiere und Säuglinge, *München. med. Wchnschr.*, 1904, li, 1497.

2. Mayerhofer, E., and Pribam, E.: Ueber die Beeinflussung der Diffusionsvorgänge an frischen tierischen Darmmembranen, *Biochem. Ztschr.*, 1910, xxiv, 453; Das Verhalten der Darmwand als osmotische Membran bei akuter und chronischer Enteritis, *Wien. klin. Wchnschr.*, 1909, xxii, 875.

3. Hamburger, F., and Sperk, B.: Biologische Untersuchungen über Eiweissresorption vom Darm aus, *Wien. klin. Wchnschr.*, 1904, xvii, 641.

an increased permeability of the intestinal tract to undigested protein in young animals. Uffenheimer's⁴ experiments led to the same conclusion.

On the other hand, Lawatschek* has recently found that the intestinal tract of very young infants is more permeable to foreign protein.

Uhlenhuth⁵ found that prolonged feeding of egg protein to rabbits caused the development of specific precipitins in the blood, thus indicating the entrance of egg protein into the general circulation. In healthy men Ascoli⁶ was able to demonstrate the presence of egg protein in the blood serum by precipitin tests as early as one and three-fourths hours after the egg was ingested. In the urine, egg protein and human protein could be demonstrated. Inouye⁷ obtained practically the same results.

Moro⁸ found milk precipitins in the blood of two out of twenty-two investigations on atrophic infants (postmortem). In one case there was complement deviation for milk protein. Bauer⁹ demonstrated precipitins and also complement deviation for milk in the blood of four atrophic infants.

In contrast to these positive results Krasnogorski¹⁰ did not find precipitable milk protein in the urine of infants suffering from nutritional disorders.

Recent experiments by Modigliani and Benini,† however, indicate that casein may be absorbed unaltered. Their technic consisted of

*Lawatschek: Die enterale Resorption von genuinen Eiweiss bei Neugeborenen und darmkranken Säuglingen, etc. *Prag. Med. Wchnschr.*, 1914, xxxix, 185.

†Permeability of Intestinal Tract of Infants for Casein of Cow's Milk, *Policlinico*, Dec. 1915, abstr. in *Jour. Am. Med. Assn.*, 1915, lxiv, 475.

4. Uffenheimer, A.: Zur Frage der intestinalen Eiweiss Resorption, *Jahrb. f. Kinderh.*, 1906, lxiv, 383.

5. Uhlenhuth: Neuer Beitrag zum spezifischen Nachweis von Eiereiweiss auf biologischen Wege, *Deutsch. med. Wchnschr.*, 1900, xxvi, 734. Haendel: Untersuchungen über die praktische Verwertbarkeit der anaphylaxie zur Erkennung und Unterscheidung verschiedener Eiweissarten, *Ztschr. f. Immunitätsforsch.*, 1910, iv, 761.

6. Ascoli, M.: Ueber den Mechanismus der Albuminurie durch Eiereiweiss, *München. med. Wchnschr.*, 1902, xlix, 398; Neue Tatsachen und neue Ausblick in der Lehre der Ernährung, *München. med. Wchnschr.*, 1903, i, 201.

7. Inouye: Ueber alimentare Albuminurie, *Deutsch. Arch. f. klin. med.*, 1903, lxxv, 378.

8. Moro, E.: Kuhmilchpräzipitin im Blute eines 4½ Monate alten, Atrophikers, *München. med. Wchnschr.*, 1906, liii, 214.

9. Bauer, J.: Ueber den Nachweis der precipitablen Substanz der Kuhmilch im Blute atrophischer Säuglinge, *Berl. klin. Wchnschr.*, 1906, xliii, 711.

10. Krasnogorski, N.: Ueber die Herkunft des Harneiweiss bei Albuminurien der Säuglinge, *Ztschr. f. Kinderh.*, 1912, iv, 526.

testing the blood serum of infants affected with gastroenteric disorders with anti casein serum from rabbits. The patients were receiving cow's milk as food.

The results obtained by means of anaphylactic tests on animals are closely analogous to those in which the precipitin test was used. Rosenau and Anderson¹¹ and others showed that the feeding of foreign protein caused the animal to become sensitized to the protein fed. This indicated that some of the protein, at least, was absorbed in a partially digested state. Vaughan, Cummings and McGlumphy¹² demonstrated, by anaphylactic tests, that rabbits absorb incompletely digested protein through the gastro-enteric tract. After feeding egg protein the blood of rabbits was capable of sensitizing guinea-pigs to egg protein. Van Alstyne and Grant,¹³ and Van Alstyne,¹⁴ found that dogs absorb foreign protein through Thiery-Villa fistulas in sufficient quantities to sensitize guinea-pigs. In a patient subject to alimentary albuminuria they found that the protein in the urine sensitized both to the foreign protein fed and to human protein. This observation is in accord with the work of Uhlenhuth and others with the precipitin test.

Lust¹⁵ has recently studied the absorption of heterologous protein by infants affected with nutritional disorders. The precipitin test applied to the urine was the means of identification, though in some cases the anaphylactic test was used. His results showed that in normal infants undigested egg or beef protein is not absorbed. In nutritional disorders he found that egg protein appeared in the urine after ingestion. Beef protein was absorbed unchanged in very few cases. The experiments of Hyashi¹⁶ and Lawatschek gave results similar to those of Lust.

Our own investigations were undertaken in the effort to determine the possibility of absorption of undigested protein by infants. For this purpose precipitin and anaphylactic tests were used and the blood was examined for the presence of reaction substances (protective ferments of Abderhalden).

11. Rosenau and Anderson: Studies on Anaphylaxis, *Bull. Hygienic Lab.*, 1908, No. 45.

12. Vaughan, Cummings and McGlumphy: The Parenteral Introduction of Proteins, *Ztschr. f. Immunitätsforsch.*, 1911, ix, 16.

13. Van Alstyne, E., and Grant, J. P.: The Absorption of Albumin Without Digestion, *Jour. Med. Research*, 1911, xxv, 399.

14. Van Alstyne, E.: Absorption of Protein Without Digestion, *Arch. Int. Med.*, 1913, xii, 372.

15. Lust: Die Durchlässigkeit des Magendarmkanales für heterologes Eiweiss bei ernährungsgestarten Säuglingen, *Jahrb. f. Kinderh.*, 1913, lxxvii, 244 and 283.

16. Hayashi, J.: Ueber die Durchlässigkeit des Säuglingsdarmes für artfremdes Eiweiss und Doppelzucker, *Monatschr. f. Kinderh.*, 1914, xii, 749.

II. ABSORPTION OF UNDIGESTED PROTEIN BASED ON THE EXAMINATION OF THE URINE BY PRECIPITIN AND ANAPHYLACTIC TESTS

In many of the experiments cited the tests for foreign protein were applied to the blood. On first thought this may seem the ideal method, but as applied to infants it has at least one insurmountable obstacle. It has been shown by Ascoli, Lust and others that the foreign protein is present in the blood stream for a very short time and the detection of its presence would require frequent examinations, obviously a procedure not permissible in infants, especially those affected with nutritional disorders. On the other hand, it has been found that the foreign protein is present in the urine over a longer period of time. The following observation made by one of us (S.) has a direct bearing on this question.

C. J. S., aged 21 years, subject to alimentary albuminuria.

The patient was given the whites of ten eggs at 8 a. m. on an empty stomach. The urine was collected every hour and blood removed at intervals of one or two hours. Two cubic centimeters of urine or citrated blood were injected into the peritoneal cavity of guinea-pigs as a sensitizing dose to test for egg protein by the anaphylactic reaction. Two weeks later the animals were given 2.5 c.c. of egg white as an intoxicating dose. Two animals, weighing from 250 to 300 gm., were used in each experiment. The results are given in Table 1.

TABLE 1.—THE PRESENCE OF EGG PROTEIN IN THE BLOOD AND URINE AFTER INGESTION OF EGG WHITE. ANAPHYLACTIC TEST

Hour	Albuminuria Heat and Acetic Acid	Anaphylactic Test Blood	Anaphylactic Test Urine
7:45 a. m.	—	—	—
8:00 a. m. egg ingested.....	—	..	—
9:00 a. m.	—	±*	—
10:00 a. m.	—	++	—
11:00 a. m.	Faint trace	—	+
12:00 m.	Heavy trace	—	++
1:00 p. m.	Marked	..	+++
2:00 p. m.	Trace	—	++
3:00 p. m.	—	..	—

* ± equals questionable reaction; + equals mild, ++ marked and +++ severe reaction.

This observation demonstrates that the foreign protein appears in the blood stream earlier, but persists in the urine for a longer time. In consideration of these results and the factors already discussed, the tests in our observations were applied to the urine.

1. *Precipitin Tests.*—The precipitating serum for egg white was obtained from rabbits in the usual way by giving three or more intravenous injections of 2.5 c.c. of egg white. The second and third injections were given at intervals of four and three days, respectively. If, after the third injection, the egg serum exhibited a titer of 1:100,000 or more, the animal was bled to death, the serum passed through a Berkefeld filter and preserved in sealed glass capsules until used. Otherwise, further injections of egg white were given until a serum of sufficient strength was obtained. No serum with a titer of less than 1:100,000 was used, and in some instances it ranged from 1:500,000 to 1:1,000,000.

In accordance with the experience of others, it was found impossible to obtain regularly a milk precipitating serum of high titer. Many animals were treated with milk, whey, casein, and the whey proteins precipitated by saturation with ammonium sulphate. One animal treated by the last method gave a serum with a titer of 1:20,000. This serum was used for tests to be described later. Further trials by the same procedure were futile, though the technic was as nearly as possible identical to that first used. Serums were obtained with titers of 1:300 to 1:700, but, owing to the negative results of Krasnogorski with such serums, they were considered inadequate.

The precipitin tests for milk were carried out on mixed specimens of urine from infants fed on cow's milk. In the egg tests the infants were fed the whites of from one to two eggs and the urine collected for six hours used for the examination. In all cases the urine was tested pure, diluted 1:5, 1:10, 1:50 and 1:100 with normal saline. Two-tenths cubic centimeter of the precipitating serum was added to each tube containing 1 c.c. of the plain or undiluted urine. The tubes were incubated at 37.5 C. for one hour and the results noted. They were placed on ice for twelve hours, and in case a definite precipitate was not apparent in the tubes considered positive after one hour incubation, the test was regarded as negative. Cases in which the precipitate appeared only after twelve hours were also considered negative. In each experiment, control tests were carried out with 0.2 c.c. of normal rabbit serum in place of the precipitating serum, and also with 0.2 c.c. of the precipitating serum added to normal urine. The urines were all faintly acid or amphoteric to litmus, and, when at all concentrated, were dialyzed through collodion for twenty-four hours before the test was applied.

DISCUSSION

The results relating to cow's milk are shown in Tables 2, 3 and 4. Judging from these results, in normal infants fed on cow's milk no foreign protein recognizable by the precipitin test appears in the urine. Two of the four atrophic infants tested excreted protein in the urine which gave a positive test with milk precipitating serum. The results in gastro-enteric disorders¹⁷ were identical. In two of the four cases

17. We make no attempt to follow any definite clinical or pathologic classification of these cases. The term gastro-enteric disorder is merely used to designate nutritional disturbances characterized by loss of weight, vomiting, loss of appetite, frequent bowel movements of more fluid consistency than normal, of abnormal color and odor. The terms mild, moderate and severe refer mainly to the general disturbances such as loss of weight or appetite, fever, vomiting and symptoms of intoxication. In the absence of a satisfactory etiologic classification we feel that it is safer and perhaps clearer to classify the cases in this way rather than to attempt classification based on pathologic lesions, the supposed infecting micro-organism or an apparent intolerance to an individual food substance.

observed a precipitate was obtained in the urine when treated with the anti- whey serum.

These results indicate, therefore, that in atrophy or gastro-enteric disorders whey protein may be absorbed from the gastro-enteric tract without complete digestion and appear in the urine. Krasnogorski, using the precipitin and complement deviation tests obtained negative results in similar observations. His precipitating serum, however, had a titer of 1:600 while ours was 1:20,000. This probably explains the difference in results. As mentioned previously, Modigliani and Benini were able to show that casein may be absorbed by infants affected

TABLE 2.—PRECIPITIN TESTS FOR COW'S MILK IN URINE OF NORMAL INFANTS

Number	Age, Months	Weight, Pounds	Albuminuria, Heat and Acetic Acid	Precipitin Reaction
1	5	14½	—	—
2	5	18½	—	—
3	6	15	—	—
4	6	15½	—	—
5	8	17	—	—
6	8	19	—	—

TABLE 3.—PRECIPITIN TESTS FOR COW'S MILK IN URINE OF INFANTS SUFFERING FROM ATROPHY

Number	Age, Months	Weight, Pounds	Albuminuria, Heat and Acetic Acid	Precipitin Reaction
1	5	9	—	Negative
2	7	8½	Faint trace	Positive pure, 1-5
3	8	8	—	—
4	9	9½	Trace	Positive pure, 1-5

TABLE 4.—PRECIPITIN TESTS FOR COW'S MILK IN URINE OF INFANTS SUFFERING FROM ACUTE GASTRO-ENTERIC DISORDERS

Number	Age, Months	Weight, Pounds	Albuminuria, Heat and Acetic Acid	Precipitin Reaction
1	3	9	Trace	Positive pure
2	6	11½	—	—
3	8	18½	—	—
4	8	13	Faint trace	Positive pure, 1-5, 1-10

with intestinal disease. The precipitin tests with egg protein are shown in Tables 5 to 10 inclusive. Tests were made on fourteen infants without symptoms of gastro-enteric disturbance. In one infant egg protein appeared in the urine after the ingestion of the whites of two eggs, although the test was negative when one egg white was ingested. In another case the test was positive when the whites of one and one-half eggs were given. In the remaining twelve normal infants there was no evidence of absorption of unaltered egg white.

These results indicate that, when given in moderate amounts, egg white is absorbed by normal infants only after complete digestion; or, to be strictly accurate, none of the foreign protein appears in the urine. Our observations differ from those of Lust in that two positive results were obtained in experiments on fourteen normal infants. His results were entirely negative.

Seven infants with mild gastro-enteric disorders were tested. (Table 6). In two cases egg protein was excreted in the urine. In one of these the test was negative after the ingestion of one egg but was positive when two eggs were given.

In three of the four cases of moderate severity tested (Table 7), positive results were obtained. Case 4 is of special interest since it was possible to make four tests at different stages of the disease. At the onset of the disease the test was negative. During the period of maximum severity the test was positive and after improvement was negative.

Of the six cases with severe symptoms all showed a positive reaction at some time during the disease (Table 8).

Six cases of eczema were investigated and the result was positive in three.

Considered collectively these results show that after the ingestion of moderate amounts of egg white normal infants rarely excrete egg protein in the urine recognizable by the precipitin test. In gastro-enteric disorders the mucous membrane becomes permeable, the degree of permeability being in direct ratio, apparently, to the severity of the disorder. These results practically coincide with those of Lust.¹⁸ Judging from the results in six cases there is a tendency for infants with eczema to absorb incompletely digested egg white.

18. In the interpretation of our results, we assume that the appearance of precipitable egg protein in the urine is indicative of its absorption in undigested or incompletely digested forms. While this assumption is in accord with accepted ideas, there are other possibilities which must be mentioned: (1) That small amounts of undigested egg protein may be absorbed but destroyed or fixed in some organ so that it does not appear in the urine; (2) that the absorption of small amounts of partially digested egg protein is usual, and the appearance of the foreign protein in the urine is not a direct indication of its absorption, but rather of the failure of the normal mechanism for its destruction.

2. *Anaphylactic Tests.*—When the urine contained coagulable protein (heat and acetic acid, cold nitric acid, tests) it was precipitated by saturation with ammonium sulphate and the precipitant removed by dialysis through collodion. A quantity of this protein solution equivalent to 3 c.c. of the urine was injected into the peritoneal cavity of a 250 to 300 gm. guinea-pig. This served as the sensitizing dose. In the absence of albuminuria 3 c.c. of the urine was used for this purpose. After the lapse of twenty-one days an intoxicating dose of 2 c.c. of egg white was given intraperitoneally. The animals were watched closely and the symptoms recorded. All equivocal reactions were excluded. The symptoms on which the degree of shock was estimated were as follows:

Mild: Uneasiness accompanied by bucking movements. Roughening of coat. Sneezing, scratching of nose, neck and forelegs. Slight to moderate dyspnea accompanied by indrawing of sides. Slight fall of temperature—1.6 to 2.5 F.

Moderate: The above symptoms in greater degree, with especial reference to fall of temperature, dyspnea and weakness.

Severe: Paralysis of hind limbs. Convulsions. Fall of temperature from 5 to 8 F. Often death. Marked distention of lungs at necropsy.

DISCUSSION

Analysis of the results shown in Tables 5 to 10 admits of the following summary:

After the ingestion of egg by normal infants, the urine did not sensitize to egg white though in two cases a positive precipitin reaction occurred.

The test was negative in two cases of mild gastro-enteric disorder, though in one of these the precipitin reaction was positive.

Of the cases of moderate severity the anaphylactic test was positive in one of three cases tested. In all three the precipitin reaction was obtained.

Eight of the severe cases were tested and in five the test was positive. In all of the urines positive with the anaphylactic test the precipitin reaction was also positive.

The urine of two of the three patients with eczema tested sensitized guinea-pigs to egg protein. In both the precipitin reaction was present.

Ten cases of malnutrition or atrophy were observed and in five the test was positive. It was never positive in the presence of a negative precipitin reaction, though in three cases with a positive precipitin test the anaphylactic reaction was absent.

The general conclusions to be drawn from the results of the two tests are identical, though the precipitin reaction was positive in a greater number of cases than the sensitization test. The precipitin reaction was often present in urines apparently free from coagulable protein (clinical tests). The anaphylactic test, however, seemed to bear a direct relationship to the presence of clinical albuminuria following the ingestion of egg. It was never possible to sensitize guinea-pigs to egg white with urine which gave no precipitate with heat and acetic

acid. In a few instances protein-containing urine did not sensitize to egg white, but in the greater number of such cases the albuminuria was entirely independent of the ingestion of egg.

Of considerable interest is the fact that human urine, free from coagulable protein, can sensitize to human protein. This fact has been pointed out by Wells,¹⁹ Uhlenhuth and others. It would thus seem that human protein derivatives below the coagulable forms are capable of sensitizing to the whole protein.

Our results offer a possible explanation for the rather contradictory results of Ascoli and others who used the precipitin test, and of Wells¹⁹ who used the anaphylactic reaction, as the means of identification of egg protein in human urine. As mentioned previously, Ascoli and others detected biologically precipitable egg protein in the blood and urine of normal individuals after the ingestion of egg. Wells, on the other hand, could not sensitize guinea-pigs to egg protein with the urine of patients who had ingested large amounts of egg white, even in instances when the urine contained small amounts of coagulable protein.

From our results it seems probable that the two tests although of the same general significance differ greatly in sensitivity, at least when applied to the identification of egg white in urine. The precipitin reaction is often positive in the presence of a negative anaphylactic test and it seems probable that the two reactions are not dependent absolutely on the same substances. This assumption is strengthened by the fact that the anaphylactic reaction was never positive in the absence of coagulable protein, which was not true of the precipitin test.²⁰

III. TESTS FOR PROTECTIVE FERMENTS (ABDERHALDEN) IN BLOOD SERUM

The work of Abderhalden²¹ and his co-workers is too well known to require any detailed description. In simplest form the theory is as follows: Foreign protein, when absorbed parenterally, stimulates the formation of certain protective substances which are capable of hydrolyzing this variety of protein. The claims of Abderhalden indicate that there is a great degree of specificity in the action of the antibody. The detection of such ferments is accomplished by digesting the suspected protein with the blood serum to be tested in a special dialyzing bag and

19. Wells, H. G.: Observations on Alimentary Albuminuria by Means of the Anaphylaxis Reaction, *Jour. Am. Med. Assn.*, 1909, lii, 863.

20. This statement applies only to the identification of egg protein in the urine, for as stated previously, human urine which contains no coagulable protein may sensitize to human protein.

21. Abderhalden, E.: *Der Nachweis blutfremden Stoffe, etc.*, *Beitr. z. klin. Infektionskrank. u. Immunitätsforsch.*, 1913, i, 243 *Abwehrfermente*, Springer, Berlin, 1914.

TABLE 5.—INFANTS FREE FROM GASTRO-ENTERIC DISEASE

Number	Age, Months	Weight, Pounds	Albuminuria	Precipitin Test	Anaphylactic Test	Remarks
1	5	10%	—	One egg white, negative.....	29 and 32. Both negative to egg; 48 hours later negative to human serum	Had severe malnutrition. Recovery.
2	6	12%	—	One egg white, negative.....	10. No reaction to egg; 48 hours later no reaction to human serum	
3	7	9%	—	One egg white, negative.....	
3, 1 week later	7	9%	—	Two egg whites + pure and 1-5	Developed intestinal disturbance 2 weeks later. Erysipelas 25 days later.
4	6	11½	—	One egg white, negative.	
4, 1 week later	11	11%	—	Two egg whites, negative.....	
5	15	16 3/16	—	One egg white, negative.....	9 and 14. No reaction to egg; 72 hours later moderate reaction to human serum	
6	8	11½	—	One egg white, negative.....	54 and 56. Negative to egg; moderate reaction to human serum 48 hours later	
7	9	14%	—	Two egg whites + pure.....	89 and 91. Negative to egg; slight reaction to human serum 72 hours later	
7, 1 week later	9	14%	—	One egg white, negative.	
8	13	16	—	Two egg whites, negative.	
9	24	—	—	Two egg whites, negative.	
10	24	—	—	One egg white, negative.	
11	24	—	—	One egg white, negative.	
12	6	11%	—	Two egg whites, negative.....	18 and 23. Negative to egg white	
13	12	17%	—	One and a half egg whites + pure, 1-5, 1-10	21 and 19. Negative to egg white; moderate reaction to human serum 48 hours later	
14	7	12 2/16	—	One and three-fourths egg whites, negative	

TABLE 6.—GASTRO-ENTERIC DISTURBANCE. MILD

Number	Age, Months	Weight, Pounds	Albu- minuria	Precipitin Test	Anaphylactic Test	Remarks
1	5	16	—	Two egg whites, positive; pure 1-5, 1-10	Six to eight green, loose stools in 24 hours; slight loss of weight; no vomiting; temperature 100 to 101 F. Condition unchanged.
1, 3 days later	5	15 11/16	—	One egg white, negative.....	Three to five greenish stools, mu- cus and soap curds; no fever or vomiting.
2	7	15	—	One egg white, negative.....	Three to six greenish, slightly loose stools; no fever or vomit- ing.
3	20	29 3/4	—	One egg white, positive; pure and 1-5	31 and 33. No reaction to egg.....	Three to six greenish, slightly loose stools; no fever or vomit- ing.
4*	6	11 1/4	—	One egg white, negative.....	Three to six greenish, slightly loose stools; no fever or vomit- ing.
5	16	19 6/16	—	One egg white, negative.....	Three to six greenish, slightly loose stools; no fever or vomit- ing.
6	6	16	—	One egg white, negative.....	Three to four slightly loose, yel- low stools; mucus; no fever or vomiting.
7*	12	19 3/4	—	One egg white, negative.....	4 and 9. No reaction to egg white; 48 hours later, slight reaction to human serum	Three to four slightly loose, yel- low stools; mucus; no fever or vomiting.

* Suffered from malnutrition before onset of diarrhea.

TABLE 7.—GASTRO-ENTERIC DISTURBANCE. MODERATE

Number	Age, Months	Weight, Pounds	Albu- minuria	Predipitin Test	Anaphylactic Test	Remarks
1*	10	10	—	One egg white, negative.....	Four to eight loose, yellow stools; mucus; temperature 100 to 102; slight prostration.
1.2 days later	10	9 6/16	—	One and a half egg whites, positive; pure, 1-5, 1-10	Four to eight loose, yellow stools; mucus; temperature 100 to 102; slight prostration.
2*	7	10	—	One egg white, positive; pure, 1-5, 1-10	36. No reaction to egg; 48 hours later, mod- erate reaction to human serum	Six to eight, yellow, loose stools; mucus; blood; temperature, 100 to 101; vomiting.
3*	6	8	—	One egg white, negative.....	Occasional vomiting; green, watery stools; temperature 100 to 102.
4	8	17	—	Albumin water as food. In- gested three to four egg whites in 24 hours; test, neg- ative	Day of onset, six watery, green stools; vomiting.
		16 11/16	Trace	Positive, pure, 1-5.....	82 and 85. Moderate symptoms to egg; 48 hours later, severe symptoms to human serum.	Second day, stools the same; no vomiting.
		16 1/4	Moderate	Positive, pure, 1-5, 1-10, 1-50...	87 and 89. Severe symptoms to egg; 80, con- vulsions, died in one half hour; 87, recovery	Frequent green stools, loose; mu- cus and blood, fourth day.
		16 6/16	No egg ingested for 48 hours; one and a half egg whites, test negative	Eighth day, marked improvement.

* Suffered from malnutrition before onset of diarrhea.

TABLE 8.—GASTRO-ENTERIC DISTURBANCES. SEVERE

Number	Age, Months	Weight, Pounds	Albuminuria	Precipitin Test	Anaphylactic Test	Remarks
1	14	16½	Trace	One egg white, negative.....	61 and 80. No reaction to egg white; severe reaction to human serum 48 hours later; 61 died in 20 minutes	*Albumin present independently of ingestion of egg.
1, 1 week later	14	15 5/16	Trace	Two egg whites, negative.....	1 and 5. No reaction to egg white; severe reaction to human serum	*Albumin present independently of ingestion of egg.
2, 2 days later	13	11 6/16	Moderate	One egg white, negative.....	3 and 11. No reaction to egg white; severe reaction to human serum	•
2, 6 days later	13	10½	Moderate	One egg white, positive pure, 1-10	•
3†	13	10 3/16	Moderate	Five-eighths egg white, positive pure, 1-5, 1-10, 1-50	100. Severe reaction; death in 40 minutes. 99. Moderate reaction; recovery; moderate reaction to human serum 62 hours later	Death 2 days later. Necropsy: enlargement and ulceration of lymphoid tissue of intestine.
4†	10	13½	Trace	One egg white, positive pure, 1-5, 1-10, 1-50, 1-100	82. Slight reaction; recovery. 80. Moderate reaction; recovery. Both moderate reaction to human serum 3 days later	*Death 6 days after test.
5	6	9	Heavy trace	Seven-eighths egg white, positive pure, 1-5, 1-10, 1-50	70. Death in 18 minutes. 76. Moderate reaction; recovery; moderate reaction to human serum 2 days later	*Death 9 days later.
5, 2 days later	7	16	—	One egg white, negative.....	*Ill 2 days.
5, 4 days later	7	15 10/16	Trace	One egg white, positive pure, 1-5	18 and 24. Moderate reaction to egg	Death 4 days later.
6	7	15 1/16	Trace	One egg white, positive pure, 1-5, 1-10, 1-50	•
	7	15	Trace	One egg white, positive pure, 1-5, 1-10, 1-50	18 and 24. Moderate reaction to egg	

* Severe general disturbances; frequent watery stools; vomiting; prostration.

† Malnutrition before onset of gastro-enteritis.

TABLE 9.—INFANTILE ECZEMA

Number	Age, Months	Weight, Pounds	Albu- minuria	Precipitin Test	Anaphylactic Test	Remarks
1*	3	12	Trace	One egg white, positive pure, 1-5 and 1-10	Severe eczema face, neck and arms.
2*	4	12½	—	One egg white, negative.....	Seborrheic eczema of scalp.
3*	4	13	Moderate trace	One egg white, positive pure, 1-5	88 and 97. No reaction to egg..... 10 and 6. Moderate reaction to egg; severe reaction to human serum.....	Eczema of face, chest and arms.
4	6	15½	Trace	One egg white, negative.....	Eczema of face, chest and arms.
5*	6	16	Trace	One egg white, positive pure and 1-5	51 and 57. Slight reaction to egg.....	Eczema of buttocks, abdomen, scalp and face.
6	7	15½	—	One egg white, negative.....	Eczema of face and scalp.

* Developed urticaria after ingestion of egg.

TABLE 10.—MALNUTRITION ATROPHY

Number	Age, Months	Weight, Pounds	Albuminuria	Precipitin Test	Anaphylactic Test	Remarks
1	3½	4½	Very faint trace	One egg, positive pure, 1-5, 1-10, 1-50	Marasmus ?
2	1	5½	Faint trace	One egg, negative.....	Albuminuria not dependent on ingestion of egg.
3	6	6½	Faint trace	One egg, negative.....	Albuminuria not dependent on ingestion of egg. Marasmus.
4	7	8	—	One egg, positive pure.....	
5	1½	6	—	One egg, positive pure, 1-5, 1-10	
6	2	6	—	One egg, positive pure.	
7	2	6 5/16	Faint trace	Two eggs, positive pure, 1-5, 1-10	
7, 2 weeks later	2½	6 5/16	—	One egg, negative.	7. Negative	
8	4	8½	Moderate trace	Two eggs, positive pure, 1-5, 1-10, 1-50	98 and 99. No reaction to egg; 24 hours later, moderate reaction to human serum
8, 2 weeks later	4½	8½	—	One egg, negative.	46 and 47. Severe reaction. 46. Death in convulsions in 20 minutes. 47. Recovered.	
9	3	7½	—	Two egg whites, negative.....	97. Negative; 29 hours later, marked reaction to human serum.	
9, 2 weeks later	3½	7½	—	Two egg whites, negative.	Moderate rickets.
10	24	17½	—	One egg white, negative.....	21 and 22. Both negative to egg white; slight reaction to human serum 48 hours later	
10, 2 days later	24	17½	—	Two egg whites, positive pure, 1-5	2 and 5. Slight reaction to egg.	
11	16	17	Faint trace	One egg white, positive pure, 1-5, 1-10	70 and 71. Severe reaction to egg; 48 hours later, moderate reaction to human serum	Otitis media. Rickets.
12	16	19½	Faint trace	One egg white, positive pure, 1-5	
13	12	17 8/10	—	One egg white, positive pure, 1-5	91 and 92. No reaction to egg; 86 hours later, slight reaction to human serum	Pertussis. Rickets.
14	24	—	One egg white, positive pure, 1-5	98. Slight (?) reaction to egg; 3 days later, moderate reaction to human serum	Rickets.
15	8	11½	Trace	Two egg whites, positive pure, 1-5	83. Severe reaction to egg; death in 30 minutes. 89. Moderate reaction to human serum; 28 hours later, moderate reaction to egg white	Otitis media.
16	9	15½	Trace	Two egg whites, positive pure, 1-5, 1-10, 1-50	

testing the dialysate for protein cleavage products. Properly controlled, a positive reaction should indicate the presence of a proteolytic ferment in the serum capable of digesting the protein used.

Assuming that the contentions of Abderhalden and his co-workers are correct, the presence of a protease capable of digesting milk in the blood serum of nurslings would indicate that undigested milk protein had been absorbed and had provoked the formation of protective ferments. It was with this hypothesis in mind that we used the test.

Technic.—The procedure of Abderhalden was carefully followed. Milk and egg protein, coagulated by heat and acetic acid, were carefully washed until free from substances capable of giving a positive ninhydrin reaction. These proteins were kept on ice in chloroform water and were tested from time to time to exclude the formation of dialyzable products.

The special dialysis bags of Schleicher and Schüll were used and each bag was tested (1) to show that it was permeable to silk peptone, and (2) that it was not permeable to the coagulated protein preparations. After use the bags were treated with boiling water and kept in sterile water under toluene. Before further use, each was again tested as mentioned above.²²

The serum was collected in the usual way and all specimens tinged to the slightest degree, with blood, were discarded. Two control tests were made with each experiment: (1) The serum heated to destroy any ferment present was dialyzed with the protein to be tested; (2) the fresh serum was dialyzed alone. Such tests should be negative.

The only departure from the technic advised by Abderhalden was the use of 0.8 c.c. instead of 1.5 c.c. of serum. This was necessitated by the smaller amounts of blood obtainable from infants.

DISCUSSION OF RESULTS

The results of the tests are shown in Tables 11 to 15, inclusive. The reaction was present often in apparently normal infants and children. It was present with greatest frequency in cases of chronic malnutrition and subacute intestinal disorders. Of interest is the fact that the serum of several infants who had never eaten egg contained a ferment capable of digesting egg protein. This finding is very difficult to explain on the basis of Abderhalden's hypothesis.

In the present state of our knowledge, a discussion of these results with any degree of assurance is impossible. Granting the correctness of Abderhalden's views, the positive tests indicate an absorption of undigested protein and have the same significance as the anaphylactic or precipitin reactions. His views, however, have not been generally accepted and there is an enormous controversial literature which it is beyond the scope of this paper to discuss. Since, therefore, the origin and function of a proteolytic ferment in the blood serum is a mooted

22. It is worthy of note that the unreliability of the dialysis bags was a tremendous obstacle in the work. A large percentage were found useless on the first tests and after use a considerable number became impermeable to peptone or permeable to the coagulated protein.

TABLE 11.—TESTS FOR PROTEASE IN BLOOD SERUM OF APPARENTLY NORMAL INFANTS AND CHILDREN

No.	Age, Months	Weight, Pounds	Protease Serum		Remarks
			Milk	Egg	
1	2	10	—	—	
2	3	11	+	..	
3	3	12	—	—	
4	4	12½	—	+	Had never eaten egg; cutaneous test neg.
5	6	16	+	—	
6	6	15	+	+	Had never eaten egg; cutaneous test neg.
7	6	14	—	..	
8	6	15	—	..	
9	7	15½	—	—	
10	8	17½	+	+	
11	10	16	—	—	
12	13	19½	—	+	
13	18	22	—	—	
14	24	24	—	+	
15	30	24½	+	—	
16	36	23	—	—	
17	36	24	—	—	
18	42	29½	+	—	
19	42	30	—	+	
20	48	32	—	—	

TABLE 12.—TESTS FOR PROTEASE IN THE BLOOD SERUM OF INFANTS AFFECTED WITH ECZEMA

No.	Age, Months	Weight, Pounds	Protease Serum		Remarks
			Milk	Egg	
1	5	12	+	+	Had never eaten egg; cutaneous test +
2	5	13	—	—	
3	5	12½	—	+	Had never eaten egg; cutaneous test +
4	5	14	+	—	
5	6	14½	—	—	
6	6	16	+	+	Cutaneous test +
7	6	15	—	+	Cutaneous test —
8	6	15½	+	+	Cutaneous test —
9	6	14½	+	—	
10	7	16	—	+	Cutaneous test —
11	7	18	+	+	Cutaneous test —
12	7	17½	—	+	Cutaneous test +
13	8	16	+	+	
14	9	17	—	—	

TABLE 13.—TESTS FOR PROTEASE IN THE BLOOD SERUM OF INFANTS SUFFERING FROM CHRONIC MALNUTRITION

Number	Age, Months	Weight, Pounds	Protease Milk	Number	Age, Months	Weight, Pounds	Protease Milk
1	4	7%	+	10	7	9%	+
2	4	8	+	11	8	10½	+
3	5	9	—	12	8	10%	—
4	5	10	+	13	8	11	+
5	6	10½	+	14	9	11½	—
6	6	11	—	15	10	12½	+
7	6	11½	—	16	10	11	+
8	7	9½	+	17	12	10½	—
9	7	10	+				

TABLE 14.—SUBACUTE INTESTINAL DISTURBANCES

Number	Age, Months	Weight, Pounds	Protease Milk	Number	Age, Months	Weight, Pounds	Protease Milk
1	3	10	+	10	7	14½	+
2	3	9	+	11	7	12½	+
3	5	14	+	12	7	14	+
4	5½	13½	—	13	8	13	+
5	6	14	—	14	8	15½	—
6	6	18	+	15	9	15	+
7	6	12½	+	16	10	13	—
8	7	14	+	17	10	14	+
9	7	18½	+				

TABLE 15.—ACUTE INTESTINAL DISTURBANCES

Number	Age, Months	Weight, Pounds	Protease Milk	Number	Age, Months	Weight, Pounds	Protease Milk
1	4	11%	—	7	8	16	—
2	6	13½	—	8	8	13½	+
3	6	14	+	9	10	14½	—
4	7	15	—	10	11	14½	—
5	7	15½	—	11	13	15½	+
6	7	14	+				

question, an attempt to attach any definite significance to its presence would savor too strongly of speculation to be profitable.

IV. SUMMARY AND CONCLUSIONS

As shown by precipitin and anaphylactic tests applied to the urine, the intestinal tract of normal infants is usually impermeable to undigested foreign protein.

In nutritional or gastro-enteric disorders, foreign protein may be absorbed in an undigested or partially digested state and appear in the urine.

The precipitin reaction, applied to the urine for the detection of egg protein, is apparently more delicate than the anaphylactic test.

These results demonstrate the possibility that certain nutritional disorders in artificially fed infants may be due to the biologic character of the food, although they obviously give no direct evidence to support such a view.

We are greatly indebted to Professor Gies for placing the facilities of his laboratory at our disposal, and to him and his associates for much assistance.

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EXPERIENCES WITH ETHYLHYDROCUPREIN IN THE TREATMENT OF MEASLES, SCARLET FEVER AND OTHER INFECTIONS *

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MINNEAPOLIS

The studies of Morgenroth and his collaborators have shown that a number of quinin derivations manifest considerable curative powers against trypanosomes, spirochetes and pneumococci, and that this power reaches its maximum in the substance known as ethylhydrocuprein.

Although this drug is very successful in curing mice affected with pneumococcus septicemia, Engwer and also one of us (H.) have been unable to obtain any striking series of cures in guinea-pigs and rabbits with experimental lobar pneumonia, even with the lowest dose (60,000 pairs per cubic millimeter) which is certainly fatal.

This drug has been used with a certain amount of success in clinical pneumonia by Linné and Vetlesen and also locally in cases of pneumococcus keratitis by Ginsberg. Giemsa and Izar have found it a specific in the treatment of stubborn estivo-autumnal malaria cases which have withstood the action of quinin.

Further extension of clinical observation with this drug in other infectious diseases was warranted; and we made tests on cases of measles and scarlet fever, using a supply of ethylhydrocuprein which had been kindly furnished to one of us by Professor Morgenroth. Our observations on scarlet fever gave negative results. Cases occurring in the contagious service of the Minneapolis City Hospital and in the private practice of one of us (S.) were treated with ethylhydrocuprein in capsules in doses of 0.1 to 0.5 gm. three times a day, according to the age of the patient. No cinchonism or other deleterious symptoms were manifested in our series. On the other hand, no beneficial effects were apparent in this series, for in the seven treated cases, the fever and acute symptoms showed an average duration of 8.9 days, while in the seven untreated cases occurring at the same time in the same hospital and in the same private practice, the average duration was 7.4 days (see Tables 1 and 2).

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In measles, however, the effects seem more promising. Eleven unselected cases were treated (Table 3) and showed an average duration of 4.3 days, while among ten unselected cases (Table 4) occurring

TABLE 1.—SCARLET FEVER, ETHYLHYDROCUPREIN SERIES

No.	Name	Age	Duration of Fever (Days)*		Max. Temp.	Principal Symptoms
			Total	After E.H.O.		
1	Rose T.	4	12	6	108.4	Red rash over entire body. Sore throat. Acute rhinitis.
2	Barty F.	7	9	7	108	Severe inflammation of throat. Rash disappeared on fourth day.
3	Max T.	7	10	8	104	Eruption extensive. Sensorium clear. Throat inflamed. No rash visible on fourth day. Slight dry cough.
4	Gladys B. ...	20	8	6	104	Rash over entire body. Throat inflamed. Sensorium clear. Eruption disappeared on third day.
5	Willis R.	16	7	5	104	Headache. Sore throat. Enlarged glands.
6	Pearl G.	31	8	6	102	Sore throat. Nausea. Pronounced angina. Enlarged glands.
7	Selma R.	25	8	5	101.5	Sore throat. Headache. Nausea. Membranous exudate.

* Average duration 8.9 days. After ethylhydrocuprein, 6.1 days.

TABLE 2.—SCARLET FEVER, CONTROL SERIES

No.	Name	Age	Duration of Fever (Days)*	Max. Temp.	Principal Symptoms
1	Gustaf C. ...	22	4	99.5	
2	Olga A.	9	5	102	
3	Leonla B. ...	29	7	104	Pain in wrists, then in entire body. Swelling of ankles. Epithelium in urine.
4	Ellen D.	23	7	101.2	Slight epistaxis. Urine negative.
5	Lillie G.	16	8	108	Pain in abdomen. Calcium oxalate in urine.
6	Louis B.	7	12	103.5	Rash over entire body. Abdomen slightly distended. Throat culture negative. Triple amorphous phosphates in urine. Also urates.
7	Alex H.	19	9	104.5	Nausea. Sore throat and delirium. Eruption faded on sixth day. Urine negative.
* Average duration 7.4 days.					
Complications—					
8	Bertha B. ...	19	12	104.5	Sore throat. Delirium. Diagnosis: scarlet fever and diphtheria.
9	Marie E.	26	10	104.5	Sore throat. Delirium. Right eye discharging. Hyaline casts in urine. Diagnosis: scarlet fever and diphtheria.
10	Agnes A.	23	4	101	Cough. R. B. C., triple phosphates and amorphous urates in urine. Diagnosis: scarlet fever and diphtheria.

under the same circumstances and during the same months of the same year, the average duration was 7.9 days. Moreover, all the treated cases were free from complications, while in the untreated

there were six cases of severe complications among sixteen consecutive cases in the Minneapolis City Hospital (Table 5), which materially lengthen the average duration of a larger series of untreated cases.

TABLE 3.—MEASLES, ETHYLHYDROCUPREIN SERIES

No.	Name	Age	Duration of Fever (Days)*		Max. Temp.	Principal Symptoms
			Total	After E.H.O.		
1	Isaac T.	5	5	5	104.8	Sore throat. Coryza. Photophobia. Slight bronchitis. Delirium.
2	Gertrude T...	7	5	8†	104.4	Sore throat. Tonsillitis. Face swollen. lacerimation
3	Mrs. H. N. ...	27	5	2	103.5	Marked coryza and lacerimation. Urine negative at all times
4	Madeline K. .	4	4	2	103	Coryza. Lacerimation. Photophobia. Bronchitis. Urine negative
5	Freddie W. ..	5	5	4	103.8	Convalescing from scarlet fever. Cough. Delirium. Hyaline and granular casts in urine first day
6	Bena H.	24	4	3‡	105	Headache and cough
7	Jerome J. ...	9	4	2	104.5	Itching of eyes and coryza. Photophobia
8	Helen V.	10	2	1	104	Itching of eyes and coryza. Cough
9	Willard L. ...	5	4	3§	104	Face swollen. Coryza. Photophobia
10	Ethel S.¶....	19	6	2	104.8	Face swollen. Severe cough. Photophobia
11	Milda H.	22	3	..	100.5	Symptomatic scarlet fever

* Average duration 4.3 days. Average duration after ethylhydrocuprein 2.6 days.

† Pneumonia. ‡ Bronchitis. § Diphtheria. || Convalescing scarlet fever.

¶ Slow beginning fever. No typical signs until the fifth day. Treatment followed by very prompt improvement.

TABLE 4.—MEASLES, CONTROL SERIES, JANUARY, 1913, TO JANUARY, 1914

No.	Name	Age	Duration of Fever (Days)	Max. Temp.	Principal Symptoms
1	Joe T.	29	4	102	Cough, nausea and rash the first day. Cough continued till fourth day
2	Sophy H.	22	9	104	
3	Charles K. ...	22	10	108	Cough throughout the period of temperature
4	Albin B.	26	3	102.6	
5	Carrie W. ...	24	3	100.2	Cough developed simultaneously with rash
6	John K.	22	5	103	Sore throat. Cough
7	Lizzie M.	30	6	102.4	Severe cough. Rash faded on fourth day
8	Victor E.	21	3	102.6	Sore throat. Cough. Cough subsided on the third day
9	Sam S.	23	3	102.4	Cough and considerable rash

In striking contrast to these cases, one of the treated patients escaped from the hospital and on being returned to the hospital after some hours' exposure showed definite signs of beginning lobar pneumonia; but these signs retrogressed and cleared up within twenty-four hours.

It cannot be stated, however, that all the results were unequivocally favorable to the idea that ethylhydrocuprein might prove a specific for the treatment of measles. The duration of the eruption was utterly unaffected by the treatment. One child (I. T.), whose sister had already been receiving ethylhydrocuprein for severe measles, became ill and was given ethylhydrocuprein by mistake by his mother at the

TABLE 5.—MEASLES, CONTROL SERIES, APRIL TO JULY, 1914

No.	Name	Age	Duration of Fever (Days)*	Max. Temp.	Principal Symptoms
1	Leroy C.	24	9	104	Coryza. Lacrimation. Slight bronchitis. Urine negative
2	Jennie L.	19	7	108	Pronounced photophobia. Urine negative
3	Paul R.	5	5†	104	Photophobia. Somnolence and some delirium
4	E. R. G.	21	10	105	Nose bleed. Sore throat. Pains in chest. Considerable coughing
5	Ed. M.	50	9	102.2	Cough. Nausea. Hiccoughs. Rash over entire body
6	Wm. H.	35	9	102.5	Rash over entire body. Urine negative
7	Lillie L.	22	8	104.5	Hard cough. Sore throat. Hoarseness. Urine negative
8	Marie H.	23	6	105	Severe headache. Sore throat. Cough. Expectorates thick yellow mucus. Pain and distention of abdomen
9	Lillian S.	21	5	100	
10	Euth N.	25	14	106.2	Severe cough throughout course

* Average duration 7.9 days.

Complications—					
11	Mrs. W. M. B.	22	7	102.5	Diagnosis: scarlet fever, diphtheria, measles
12	Floyd B.	17	17	104.5	Sore throat; chills. Diagnosis: scarlet fever, measles
13	Arthur P. ...	21	21	104.7	Headache, cough, nausea. Diagnosis: scarlet fever, diphtheria and measles
14	Eleanor E. ...	4	6‡	108	Erasche. Coryza. Cough. Diagnosis: mastoiditis, bronchitis
15	Mrs. S. E. ...	40	3‡	100	Very stupid; restraint necessary. Involuntary voiding of urine. Albumin, casts and pus cells in urine. Diagnosis: scarlet fever, diphtheria, measles
16	Chester I. ...	7	15‡	103.5	Rash on face and neck only. Pronounced coryza; eyes swollen; inflamed throat and cough. Diagnosis: pleural pneumonia, measles

† Hemorrhagic type.
measles.

‡ Mastoiditis and bronchitis.
§ Pleural pneumonia, measles.

§ Scarlet fever, diphtheria.

first outbreak of symptoms. In spite of this early treatment, which was continued throughout the febrile period, his illness was of moderately severe grade, his fever lasted five days, and his eruption and other symptoms were in no wise mitigated. In most of the cases, however, the fever fell and toxic symptoms abated markedly soon after the installation of treatment.

The series of cases treated thus far is too limited to warrant the drawing of conclusions,¹ but in view of the difficulty of obtaining a sufficient supply of the drug under present European conditions, it has seemed to us worthy of being placed on record as a preliminary publication; it indicates that ethylhydrocuprein is worthy of further trial in the treatment of measles.

The experiments of Valenti and of Moon on the favorable effects of quinin in rabies made it seem possible that ethylhydrocuprein might prove of value in this and in other infections due to filterable viruses. One of us has tried it in experimental rabies (in collaboration with Dr. McDaniell of the Minnesota Public Health Service), experimental vaccinia, and in collaboration with Drs. Herman Binger and Murray (Minneapolis), in a few cases of trachoma. In all these conditions, however, no effect was noted.

Morgenroth, J., and Halberstaedter, L.: Zur Kenntnis der Chininwirkung, *Berl. klin. Wchnschr.*, 1910, xlvii, 646; Ueber die Heilwirkung von Chininderivaten bei experimenteller Trypanosomeninfektion, *ibid.*, 1911, lviii, 1558.

Morgenroth, J., and Levy, R.: Chemotherapie der Pneumokkeninfektion, *ibid.*, 1911, xlviii, 1560, 1979.

Morgenroth, J., and Kaufmann, M.: Zur Chemotherapie der experimentellen Pneumokokkeninfektion, *Zentralbl. f. Bakteriol.*, 1912, liv, Ref. Beilage 69.

Gutmann, L.: Zur experimentellen Chemotherapie der Pneumokokkeninfektion, *Ztschr. f. Immunitätsforsch.*, 1912, xv, 625.

Rosenthal, F., and Orien: Zur experimentellen Chemotherapie der Pneumokokkeninfektion, *ibid.*, 1914, xx, 572.

Rosenthal, F.: Zur Chemotherapie der Experimentellen Pneumokokkeninfektion, *Berl. klin. Wchnschr.*, 1914, li, 573.

Hirschfelder, A. D.: Unpublished experiments.

Vetlesen, H. J.: Ueber die chemotherapeutische Behandlung einiger Fälle von Pneumonie mit Aethylhydrocuprein, *Berl. klin. Wchnschr.*, 1913, l, 1473.

Lenné: Zur Behandlung der Pneumonie mit Aethylhydrocuprein und Pneumokokkenserum, *ibid.*, 1913, i, 1976.

Ginsberg, S., and Kaufmann, M.: Beeinflussung der kornealen Pneumokokkeninfektion beim Kaninchen durch Chinaalkaloide, *Klin. Monatsbl. f. Augenh.*, 1913, N. F., xv, 804.

Goldschmidt, M.: Zur Spezifischen Therapie der Pneumokokkeninfektion des menschlichen Auges, besonders des *Ulcus corneae serpens*, durch Aethylhydrocuprein, *ibid.*, 1913, N. F., xvi, 449.

Giemsa, G., and Werner, H.: Erfahrungen mit Weiterem dem Chinin nächstehenden Alkaloiden und einigen ihrer Derivate bei Malaria, *Beihefte z. Arch. f. Schiffs und Tropenhygiene*, 1914, xviii, 81.

Izar, G., and Nicosia, R.: Ueber Chemotherapie bei Malaria, *Berl. klin. Wchnschr.*, 1914, li, 385.

Valenti, A.: Azione della chinine sul virus rabido, *Boll. Soc. Med. e Chir. di Pavia*, 1904, iv, 38.

1. Experimental measles has been produced in the monkey by Anderson and Goldberger, but Professor Anderson has assured us that in this animal the disease is too mild and the infection too uncertain to furnish as satisfactory evidence of therapeutic results as can be obtained in the clinic.

Moon, V. H.: The Effect of Quinin on Rabies in Dogs, *Jour. Infect. Dis.*, 1913, xiii, 165. Since this article was written there have appeared also:

Frothingham, L., and Halliday, J.: Effect of Quinin on Rabbits Inoculated with Rabies, *Jour. Infect. Dis.*, 1914, xxx, 275.

Krumwiede, C., and Mann, A. G.: The Effect of Quinin in Rabies, *Jour. Infect. Dis.*, 1915, xvi, 24.

Moon, V. H.: Further Observations on the Effects of Quinin in Rabies, *ibid.*, 1915, xvi, 58, which contradict Moon's first observations.

REPORT OF A CASE OF PROLONGED ANURIA WITH FEW SYMPTOMS *

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LEAD, S. D.

Mamie R., 7 years old. Premature at 6½ months, raised in an incubator and fed on malted milk. Teething was normal. She walked at 13 months, but was always a tiny baby. She was never sick during childhood, but was always delicate.

On March 3, 1914, she was taken with an attack of scarlet fever, so mild that it would have been overlooked, but for the fact that another more marked case appeared in the same family. All during the attack she passed but little urine, an average of 1½ ounces daily. On March 23 she came under my care. Physical examination at that time was negative; there was no edema nor symptoms of any description except the scanty urine. Mentally she was very bright, and continued so throughout the time reported on. The child was very thin and it was possible to palpate the entire abdomen thoroughly.

The following table represents the actual amount of urine passed over a prolonged period:

Date	Ounces	Date	Ounces
March 23.....	1½	April 22.....	4
March 29.....	3	April 24.....	2
March 31.....	2½	April 26.....	3
April 3.....	30	April 27.....	1
April 5.....	3	April 28.....	3
April 6.....	1¾	April 29.....	4
April 7.....	3	May 1.....	1½
April 8.....	4	May 3.....	3
April 9.....	2	May 5.....	3
April 12.....	2	May 6.....	3
April 15.....	1¾	May 7.....	3
April 16.....	2½	May 8.....	*
April 17.....	½	May 9.....	8
April 19.....	3		

* Profuse.

From this time on the amount increased very rapidly and by the end of the following week had reached normal. On only one examination were any casts found, and then two granulars appeared. No albumin was ever detected.

This was an extremely interesting case, because the anuria seemed to have no influence on the patient's condition. At only one time did she have a convulsion and then it was not very severe. The parents of this child were very intelligent, and I am positive they did not overlook the least amount of urine passed.

When the amount on April 3 jumped to 30 ounces, we were satisfied that she had a retention, but we are of the opinion now that subsequent events showed this not to be the case. All kinds of treatment were tried: the salt-free diet, the Fischer hypertonic salt treatment, and the use of thyroid, diuretics, hot packs, etc., the only demonstrable results being no change for the worse.

The little girl was in perfect health soon after these data were compiled, and has remained so ever since. Repeated examinations of the urine in the last two years have failed to find anything pathologic.

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PROGRESS IN PEDIATRICS

REVIEW OF NEUROLOGY IN CHILDHOOD FOR 1914-1915

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CEREBROSPINAL FLUID

The latest conception regarding the manner of formation of cerebrospinal fluid is that it is a product of the secretory activity of the epithelium of the choroid plexus. Drugs which stimulate glandular secretion are supposed to increase the formation of cerebrospinal fluid. Using chlorbutanol as an anesthetic, Dandy and Blackfan¹ trephined the Atlas and inserted a special fitting cannula. The animal was so placed that the cannula formed the dependent part. A steady outflow of cerebrospinal fluid was thus obtained, after allowing the accumulated fluid to escape. Jugular compression, by production of cerebral venous stasis, caused an instantaneous increase of cerebrospinal fluid. Ether also caused an increased production of fluid. Amyl nitrite had no such effect. Pilocarpin produced a constant but very slight increase. Intravenous injections of freshly prepared aqueous extracts of choroid plexus and of posterior lobe of pituitary body failed to produce any increase. Following the pilocarpin experiments, the choroid plexuses were removed for histological study. No alterations which could be ascribed to glandular activity were observed.

"One of the strongest arguments in favor of the secretory theory of cerebrospinal fluid formation is the difficulty with which foreign substances pass from the blood to the cerebrospinal fluid." Of several substances tried, hexamethylenamin and salicylic acid were the only substances which Dandy and Blackfan could demonstrate in the spinal fluid after oral, subcutaneous and intravenous administration. Flooding the blood with colored solutions, such as indigo, carmin, trypan blue, and phenolsulphonephthalein failed to show even a trace in the cerebrospinal fluid. These investigators further state:

"The behavior of the Wassermann reaction in the cerebrospinal fluid of hereditary syphilis, without involvement of the central nervous system, gives further evidence of the impermeability of the choroid plexus to foreign substances. In the majority of patients whom we

1. Dandy, W. E., and Blackfan, K. D.: *AM. JOUR. DIS. CHILD.*, 1914, viii, 406.

examined, the reaction was positive in the blood, but in no instance was there a positive reaction in the cerebrospinal fluid." Summarizing the views on the production of cerebrospinal fluid, they think probable that "cerebrospinal fluid is formed both by filtration and secretion."

Dandy and Blackfan studied the absorption of cerebrospinal fluid by substituting phenolsulphonephthalein solution for cerebrospinal fluid. The excretion of the dye was determined in the urine, blood and lymph. It was detected in the blood in three minutes, whereas there was no trace in the lymph for forty-five minutes. It appeared in the urine in five minutes. The greatest amount of absorption occurs from the spinal subarachnoid space, there being practically no absorption from the ventricles.

They were unable to find evidence supporting the existence of stomata in the subarachnoid space. India ink and lamp black granules substituted for cerebrospinal fluid, even when injected under a pressure of 100 mm., failed to show any passage of granules into the blood.

Grulee and Moody² take exception to the statement made by Miller and Levy that the Lange "gold chlorid reaction has no advantages over known laboratory proceedings in the diagnosis of congenital syphilis." They obtained characteristic reactions in the 1 to 40 and 1 to 80 dilutions in eighteen cases of congenital syphilis. In meningitis, reactions occur in the higher dilutions.

"Brain tumors, toxic meningitis (meningismus), edema from sun-stroke, uremia, etc., may give a slight reaction in the fourth, fifth and sixth tubes (1 to 80, 1 to 60 and 1 to 320) when they react at all. The reactions in this group are rarely stronger than a dark blue and usually lie between a red blue and a violet."

Neisser and Friedman had previously shown that other inorganic colloids besides gold chlorid could be used in the same manner. Emanuel³ adopted a Mastix solution, which is easily prepared. Five tubes are used for the test. In the first tube 1.5 c.c. of a 1.25 per cent. salt solution is placed. Only 1 c.c. is put in the other tubes. To the first tube, 0.5 c.c. of spinal fluid is added. After thoroughly mixing, 1 c.c. of the mixture in the first tube is added to the second, 1 c.c. of the second to the third, and so on. None of the mixture is put in the fifth tube. One c.c. of the Mastix solution is added to each tube. The reaction is read at the end of twelve hours. With normal spinal fluids, no precipitation occurs in the first four tubes, indicating the presence of a protective colloid. In syphilis of the brain and tabes, precipitation occurs in all five tubes.

2. Grulee, C. G., and Moody, A. M.: *AM. JOUR. DIS. CHILD.*, 1915, ix, 17.

3. Emanuel, G.: *Berl. klin. Wchnschr.*, 1915, lii, 793.

Major and Nobel⁴ find the glycol tryptophan reaction a valuable addition to the diagnostic measures used in meningitis. The test determines the peptolytic power of cerebrospinal fluid. In no case without meningitis did these observers obtain a positive reaction. Various dilutions, up to 1 to 200, are made. One c.c. each of the fluid and glycol tryptophan are placed in a test tube, and 1 c.c. toluene added as a preservative. The mixture is incubated for three hours. A few drops of dilute acetic acid are added, and then a small amount of oversaturated calcium chlorid, to be briskly shaken just before using. In the presence of free tryptophan a red color is obtained.

Segagni⁵ found the test constantly negative in eight cases of tuberculous meningitis, one of cerebral hemorrhage, and one of cerebellar tumor.

The value of the Meyerhofer test for spinal fluid is confirmed by Lackner and Levinson.⁶ The test consists in determining the amount of decinormal permanganate solution reduced by 1 c.c. of cerebrospinal fluid when boiled for ten minutes in a strongly acid medium.

Lemchen⁷ describes a new method of staining cells in the cerebrospinal fluid. Two solutions are prepared. Solution 1 is 2 per cent. benzidin in glacial acetic acid. Solution 2 is hydrogen peroxid. The two solutions are mixed in a small test tube before using. A white cell pipet is used to make the dilution. "Draw the stain to 0.5 and spinal fluid to 11. Mix and count." Red blood cells are stained blue, polymorphonuclears are stained light yellow, while the nucleus is visible by having blue granules in it. In lymphocytes the periphery is stained, appearing as a dark-blue ring.

The reduction of Fehling's solution in the cerebrospinal fluid has been utilized for diagnostic and prognostic purposes. DuBois and Neal⁸ state that while the absence of reduction is of marked significance, its presence means nothing. Equal quantities of cerebrospinal fluid and Fehling's solution should be used. These observers obtained reduction in 73 per cent. of tuberculous fluids. Abramson⁹ thinks the test has definite prognostic value not only in poliomyelitis but in other pathologic conditions. "A fluid that does not reduce Fehling's solution indicates an extensive and severe pathologic change." When the reducing power returns, improvement follows.

4. Major, R. H., and Nobel, E.: *Arch. Int. Med.*, 1914, xiv, 383.

5. Segagni, S.: *LaPediatria*, 1914, xvii, No. 12.; abstr., *Jour. Am. Med. Assn.*, 1915, lxiv, 285.

6. Lackner, E., and Levinson, A.: *Arch. Pediat.*, 1915, xxxii, 508.

7. Lemchen, B.: *Med. Rec.*, New York, 1915, lxxxviii, 443.

8. DuBois, P. L., and Neal, J. B.: *AM. JOUR. DIS. CHILD.*, 1915, ix, 1.

9. Abramson, H. L.: *AM. JOUR. DIS. CHILD.*, 1915, x, 344.

Auer¹⁰ studied the functional effect of experimental intraspinal injections of serums with and without preservatives. He endeavored thereby to determine the explanation for the occasional fatalities following the use of antimeningitis serum. Auer shows that one of the main dangers seems to be the increased intraspinal pressure, as has been suggested by Flexner. That this factor of increased pressure is a prominent one, is shown by the injection of a few cubic centimeters of tricesol serum after the previous introduction of plain horse serum. A stoppage of respiration, broken occasionally by short gasps, occurs; a profound drop in blood pressure, and a marked slowing of the pulse. The removal of spinal fluid in such an instance suffices to restore pulse, blood pressure and respiration to their normal condition. Auer recommends that one be prepared to remove part of the injected fluid, and to administer artificial respiration. He suggests the use of a preservative which could be removed just before injection. Ether seems preferable to chloroform.

DuBois and Neal also think that the cause of fatalities following intraspinal injection of serum is probably "due to injudicious administration of the serum—too large dose, or too rapid increase of pressure, which is likely to happen unless the gravity method is used—or to an unusual susceptibility on the part of the patient." They also note that similar fatalities have been reported from France, "where serum without preservative is used."

Fonzo¹¹ records the occurrence of a respiratory failure during lumbar puncture which was performed on a child with meningitis. He explains the death by a probable "hyperemia ex vacuo" in the bulbar region. In order to facilitate the entrance of the trocar, the head was strongly flexed forward, probably causing a sudden displacement of cerebrospinal fluid forward.

Quincke¹² discusses the various indications for lumbar puncture. In acute cases of serous meningitis, lumbar puncture may effect a cure. Brain tumor is no contraindication for lumbar puncture. On the contrary, if carefully done, it may be beneficial, even causing a subsidence of choked disk.

Smith¹³ and Lapage¹⁴ report their experiences with lumbar puncture in the diagnosis and treatment of nervous diseases in childhood.

10. Auer, J.: *Jour. Exper. Med.*, 1915, xxi, 43.

11. Fonzo, F.: *LaPediatria*, 1914, xxii, 286.

12. Quincke, H.: *Therap. Monatsh.*, 1914, xxviii, 469.

13. Smith, F. H.: *South. Med. Jour.*, 1915, viii, 858.

14. Lapage, C. P.: *Med. Chron.*, 1914, xxvii, 227.

MENINGITIS

Bardth¹⁵ recommends the surgical treatment of purulent meningitis by lumbar laminectomy and drainage of the dural sac. The usual picture of meningitis observed at necropsy has made us skeptical in regard to the probable usefulness of any surgical measures. Bardth reminds us that a similar line of reasoning prevented us heretofore from treating peritonitis surgically.

Despite the bad results thus far obtained by drainage of the cisterna magna, Kopetzky¹⁶ believes that in purulent meningitis such an operation may prove a useful measure. He urges that the operation should not be entirely discarded.

Leighton and Pringle¹⁷ report two cured cases of streptococcus meningitis, treated surgically. One of these was in a child, aged 8 years. Lumbar laminectomy over the third lumbar vertebra was followed by complete recovery.

DuBois and Neal,¹⁸ reporting a complete recovery from streptococcus meningitis, disapprove of operative measures and think that Haynes' advice to operate on all patients with septic meningitis is quite unjustifiable.

Herman¹⁹ reports a case of pneumococcus meningitis in a sixteen-day-old infant. It was admitted to the hospital with a subnormal temperature. The physical examination was negative. Death occurred after twenty-four hours. A necropsy showed the presence of pneumococcus meningitis.

Mauriac and Philip²⁰ report a case of pneumococcus meningitis which developed one month after scarlet fever. The child, 8½ years old, was taken sick with vomiting and epileptiform movements of the left side, followed by fever and coma. The urine contained a large amount of albumin, the blood and spinal fluid a large amount of urea. The second lumbar puncture revealed a pneumococcus meningitis.

Krever²¹ distinguishes two forms of pneumococcus meningitis, differing in their origin and prognosis. The variety complicating a pneumonia is more fatal than that following nasopharyngitis.

Favorable results obtained by the use of ethylhydrocuprein in various pneumococcus infections have been reported by numerous observers during the past eighteen months. From the neurological viewpoint, it is encouraging to read of even a rare cured case of pneumococcus meningitis.

15. Bardth: *Arch. f. klin. Chir.*, 1914, cv, 653.

16. Kopetzky, S. J. *Laryngoscope*, 1914, xxiv, 733.

17. Leighton, W. E., and Pringle, J. A.: *Jour. Am. Med. Assn.*, 1915, lxiv, 2054.

18. DuBois, P. L., and Neal, J. B.: *Arch. Pediat.*, 1915, xxxii, 28.

19. Herman, C.: *Arch. Pediat.*, 1915, xxxii, 583.

20. Mauriac, P., and Philip, P.: *Ann. de méd. et chir. inf.*, 1914, xviii, 475.

21. Krever, A. R.: *Russk. Vrach.*, abstr., *Jour. Am. Med. Assn.*, 1914, lxiii, 2170.

Loewe and Meyer²² report two cured cases of pneumococcus meningitis by the administration of ethylhydrocuprein. They gave 5 c.c. of a 1 per cent. solution intraspinally.

Leschke²³ states that Wolff had a recovery in an 8 months old baby with this drug.

Boland,²⁴ Terbutt,²⁵ Alan Brown,²⁶ Ely,²⁷ Hill and Packard²⁸ report cases of influenzal meningitis. Of the five patients reported by Hill and Packard, one survived. All the other cases terminated fatally.

Atkinson²⁹ reports a case of meningitis associated with an influenza-like bacillus. Besides the gram-negative bacilli, long wavy filaments and twisted spirals were observed. The finding suggests the possibility that some of the so called leptothrix forms sometimes seen in the spinal fluid from patients with meningitis, are, in reality, aberrant forms of *Bacillus influenzae*.

A singular case of meningitis in a two week old infant is reported by Garmer and Havelocque.³⁰ The spinal fluid showed the typhoid bacillus. The child was breast fed, and the mother gave no past history of typhoid infection.

Goebel³¹ reports a proteus meningitis in a new-born child. The clinical picture was that usually seen with any form of meningitis. A pure culture of *Bacillus proteus* was obtained from the spinal and ventricular fluid. The blood serum of the patient agglutinated the organism in a 1 to 60 dilution but did not agglutinate a stock culture of *Bacillus proteus*. The child presented an odor similar to that given by the organism growing on culture media.

Rutelli³² reports a case of streptothrix meningitis in a 6 months infant. The organism was cultivated in pure culture on Bordet-Gengou media.

A puzzling case of recurrent meningitis due to lead in a child of 5 years is reported by Thomas and Blackfan.³³ The patient was taken sick five days before admission to the hospital with characteristic symptoms. A lumbar puncture brought clear sterile fluid, cells 20-40,

22. Loewe, E., and Meyer, F.: Berl. klin. Wchnschr., 1915, lii, 1018.

23. Leschke, E.: Deutsch. med. Wchnschr., 1915, xli, 1359.

24. Boland, C. V.: Lancet, London, 1915, clxxxix, 704.

25. Terbutt, A. H.: Med. Jour. Australia, abstr., Rev. Neurol. and psychiat., 1915, xiii, 33.

26. Brown, Alan: Canad. Med. Assn. Jour., 1915, v, 1076.

27. Ely, F. A.: Jour. Iowa State Med. Soc., 1915, v, 391.

28. Hill, R. B., and Packard, R. J.: Lancet-Clinic, 1915, lxiii, 723.

29. Atkinson, E.: Med. Jour. Australia, 1914, i, 415, abstr. Rev. neurol. and psychiat., 1915, xiii, 34.

30. Garmer, M., and Havelocque, Mme.: Nourisson, 1914, ii, 211.

31. Goebel, F.: Deutsch. Arch. f. klin. Med., 1914, cxvi, 119.

32. Rutelli, G.: LaPediatria, 1915, xxii, 713.

33. Thomas, H. M., and Blackfan, K. D.: AM. JOUR. DIS. CHILD., 1914, viii, 377.

mononuclears predominating, globulin reaction positive. Fehling's solution was reduced. The Wassermann and Von Pirquet reactions were negative. The patient was discharged well after a month. Five months later, the patient was readmitted with a similar trouble. A lead line was noticed on the gums. Examination of the red blood cells showed characteristic stippling. The source of the lead was soon explained when the child's mouth was found covered with lead paint from his crib. The patient was discharged well. Three weeks later convulsions recurred, followed by death. No necropsy was done.

Jovane³⁴ records what he terms "a chronic form of meningitis" which usually ends in recovery after a number of months. During the disease a tremor is noticed. It is followed by various degrees of contractures. Other than slight pleocytosis, the spinal fluid appears normal. The etiology is unknown.

The pathologic findings of a case of pachymeningitis hemorrhagica interna, undiagnosed during life, are given by Riley.³⁵ The clinical diagnosis was "decomposition" and internal hydrocephalus. Wilcox³⁶ studied the value of Macewen's sign in the diagnosis of meningeal conditions. He found the sign present in sixty-seven of seventy-one patients who had meningitis. It was also present in all of five patients with acute poliomyelitis. Macewen's sign is best determined by the stethoscope placed on the forehead just above the base of the nose. The skull is percussed directly over the parietal region, the percussing finger going from a point just over the parietal boss to that at which the stethoscope is applied.

In "a summary of four years' clinical and bacteriologic experience with meningitis in New York City," DuBois and Neal select four signs as the most important in the diagnosis of meningitis. These are stiffness of the neck, variations of regularity in rate and depth of respiration, Macewen's sign and Brudzinsky's sign.

The differential points in the diagnosis of cerebral intoxication, meningismus and meningitis, pachymeningitis and encephalitis are emphasized by Heiman.³⁷ The difference between intoxication and serous meningitis, he notes, is only one of degree.

The symptoms of meningismus are frequently seen after decompression operations, according to Minz.³⁸ These symptoms are due to an increased amount of cerebrospinal fluid. They are especially seen following operations for tumors of the posterior cranial fossa.

34. Jovane, A.: *LaPediatria*, 1914, xxii, 181.

35. Riley, F. B.: *Tr. Chicago Path. Soc.*, 1915, ix, 233.

36. Wilcox, H. B.: *Arch. Pediat.*, 1915, xxxii, 909.

37. Heiman, H.: *Arch. Pediat.*, 1915, xxxii, 579.

38. Minz, V. M.: *Russk. Vrach.*, 1914, xiii, Nos. 13 and 14, abstr., *Jour. Am. Med. Assn.*, 1914, lxiii, 616.

DuBois and Neal have never seen a case of meningitis follow one of meningismus. They believe that meningismus is a functional condition, probably of toxic origin.

Guinon³⁹ maintains that the term meningitis is used rather indiscriminately to cover many conditions associated with cerebral irritation, in which meningeal inflammation does not actually exist. A number of conditions so designated are cases of encephalitis. He quotes the admirable description of encephalitis by Comby and Chartier. Guinon thinks this picture should be made more flexible. Encephalitis may be mild or severe. He reports in detail two instances of encephalitis which recovered. The first, a child 4 years old, with a good family history, was taken sick after a normal convalescence from measles. One afternoon during her play the child fell, due to weakness of her extremities. Three days later she developed a train of symptoms characteristic of encephalitis. These consisted of gradually increasing stupor, inertia and apparent unconsciousness. The motor phenomena were general rigidity, contractures of the extremities, especially on the left side, exaggerated reflexes, partial athetosis and tremor. There was no Kernig's sign or any definite rigidity of the neck. The eyes were normal. Cerebrospinal fluid was normal. This period lasted for six days, and was followed by a period of aphasia lasting ten days. About the thirtieth day convalescence began and continued rapidly. In less than ten days speech returned and movements of the extremities became normal. Recovery was complete, except that there persisted a slight degree of facial asymmetry noted during laughter. The pathogenesis remains obscure. Rarely, a microorganism may be isolated, but the majority of investigators attribute the disease to a toxic origin. Guinon is unwilling to admit that the measles which the child had several weeks before the onset of this encephalitis played any rôle in the etiology of this particular case. He discusses the possibility of encephalitis being a manifestation of poliomyelitis.

MENINGEAL COMPLICATIONS OF THE CONTAGIOUS DISEASES

For persistent convulsions which occurred during the course of pertussis, which were refractory to chloral and chloroform, Fischer⁴⁰ performed ventricular aspiration. Immediate recovery followed.

Four cases of paralysis in pertussis are reported by Sorensen,⁴¹ who discusses their probable causes. Their rapid disappearance spoke against hemorrhage as a cause, especially since the paralysis occurred during the quiescent stage of the disease. He therefore considered them of toxic origin.

39. Guinon, L.: *Arch. de méd. d. enfants*, 1914, xvii, 561.

40. Fischer, L.: *New York Med. Jour.*, 1914, c, 1054.

41. Sorensen, S. T.: *Arch. f. Kinderh.*, 1915, lxiv, 368.

Weigert⁴² records the occurrence of meningocele in an infant of 4 months as a rare complication of pertussis. After recovery the tumor slowly receded.

Wharton-Smith⁴³ notes that text books do not refer to acute myelitis among the sequelae of varicella, and reports such a case. Two weeks after the onset of the varicella the patient's temperature began to rise, and it was noticed that the patient's legs were drawn up. He was unable to move either of his legs or his left arm. There was also loss of sensation over these extremities. Sensation gradually returned after two weeks. His left arm was held over his head and he would scream with pain, if one attempted to pull it down or to straighten his legs. Incontinence of urine and feces was present. Fourteen months later the patient was again seen. He was able to play. There was still some spasticity of the lower extremities. The reflexes were active. There was no evidence of urinary incontinence excepting nocturnal enuresis, from which he had suffered prior to his acute illness.

The occurrence of transitory ataxia in a 7 year old boy during convalescence from measles is considered by Morichau⁴⁴ as another example of acute encephalitis, such as described by Guinon.

Rolleston⁴⁵ reports a case of extensive occlusion of the cerebral arteries following diphtheria. Two weeks after the onset of pharyngeal diphtheria the patient, an eight year old girl, complained of pain in her left chest. As her heart was being examined, she became cyanotic and unconscious, had convulsive movements of the right arm and leg, and Cheyne-Stokes respiration. The corneal reflex was absent on the right side, but active on the left side. Paralysis of the muscles of deglutition followed. Two days later death occurred. The necropsy revealed a clot filling the basilar artery, which Rolleston remarks, from his observation of eighteen cases, is the most common lesion in diphtheritic hemiplegia.

Mollet⁴⁶ collected and studied the cases of organic hemiplegia of diphtheritic origin. It occurs once in 1,500 cases. It usually follows malignant diphtheria, occurring in the second or third week. In two-thirds of the patients the hemiplegia is right sided. The prognosis is grave, not alone because of permanent contractures which follow, but on account of the high mortality, one third of the patients succumbing to the attack.

42. Weigert, R.: *Monatsch. f. Kinderh.*, 1914, xiii, 139.

43. Smith, Wharton: *AM. JOUR. DIS. CHILD.*, 1915, x, 444.

44. Morichau, R., et al.: *Soc. méd. d. Hôp.*, July 3, 1914, abstr., *Arch. de méd. d. enfants*, 1915, xviii, 615.

45. Rolleston, J. D., and Guinon, E. B.: *Rev. neurol. and psychiat.*, 1915, xiii, 373.

46. Mollét, A.: *These de Paris*, abstr., *Arch. de méd. d. enfants*, 1915, xviii, 403.

POLIOMYELITIS

Gegenbach,⁴⁷ Whitman,⁴⁸ Amesse,⁴⁹ Andrews⁵⁰ and others discuss poliomyelitis.

Flexner^{51, 52} and his co-workers studied the mode of infection in poliomyelitis. They demonstrated that the virus readily reaches the central nervous system when brought into relation with peripheral nerves. Much larger quantities are necessary to produce poliomyelitis if the virus is introduced into the blood stream. The lesions in human poliomyelitis seem to correspond with those caused by intraneural and not by intravenous inoculation. Flexner considers the respiratory tract the "infection atrium" in this disease. Flexner was able to prevent the development of poliomyelitis in monkeys by the intraspinal injection of immune monkey serum. The spread of poliomyelitis is effected by the existence of healthy carriers, such having been demonstrated in the parents of an infected child and in recovered patients. There are also cases of nonparalytic ambulant forms. This has not only been proved clinically, but by the detection of changes in the cerebrospinal fluid, by the demonstration of neutralizing principles in the blood of such patients and by the determination of the virus of poliomyelitis in the upper respiratory tract.

Fraser⁵³ studied ninety cases of acute epidemic poliomyelitis. The symptoms usually encountered are feverishness, drowsiness, restlessness, twitching of extremities, sweating, vomiting and anorexia, rigidity of the neck, pain and tenderness, either generalized or localized to the limb involved. Similarly, the twitching may be confined to the extremity which is later paralyzed. The paralysis may involve the extremities, singly or combined, or may be respiratory or facial. Tuberculous meningitis and specific myelitis occasionally give the same clinical picture as well as cerebrospinal fluid findings as are noted in poliomyelitis. During the acute stage treatment has proven of no avail. After the acute stage massage will do much to improve paralyses. The importance of electricity is only secondary to that of massage and passive exercises.

Abramson examined the cerebrospinal fluid of forty-three patients with acute poliomyelitis. Fifteen showed a great increase in the cell count, twenty-four showed a moderate increase, four showed no increase. The lymphocytes were in excess in all but five fluids. These

47. Gegenbach, F. P.: *Colorado Med.*, 1915, xii, 21.

48. Whitman, R. C.: *Colorado Med.*, 1915, xii, 20.

49. Amesse, J. W.: *Colorado Med.*, 1915, xii, 17.

50. Andrews, L. E.: *Jour. Oklahoma State Med. Assn.*, 1914, vii, 56.

51. Flexner, S., and Amoos, H. L.: *Jour. Exper. Med.*, 1914, xx, 249.

52. Flexner, S.: *AM. JOUR. DIS. CHILD.*, 1915, ix, 353.

53. Fraser, F. R.: *Am. Jour. Med. Sc.*, 1914, cxlviii, 1.

five showed a polymorphonuclear pleocytosis. Abramson calls attention to the importance of large endothelial cells, and cells with pyriform nuclei. When he finds the former in large numbers he very strongly considers poliomyelitis. The cell count and globulin reaction in Abramson's examinations show a parallel relationship, contrary to what has been stated by the Rockefeller Institute workers. There exists an inverse relation between the amount of globulin and the reduction of Fehling's solution.

Sawyer⁵⁴ made an epidemiologic study of poliomyelitis in northern California. He demonstrated the active virus of poliomyelitis by animal inoculation in the rectal washings from a patient fourteen days after the onset of the paralysis.

Netter⁵⁵ reports his results obtained in the treatment of acute poliomyelitis by the use of serum obtained from individuals who have had the disease. He used the serum intraspinally in doses of 5 to 13 c.c., repeating the dose daily for eight consecutive days. Early administration is necessary, "from the first to the fourth day." Of thirty-two cases treated in this manner, six were completely cured, three were practically cured, twelve were improved, three were unchanged, eight died.

Alfaro and Hitce,⁵⁶ following Netter's technic, treated an acute case of poliomyelitis in an infant of 7 months. On the fourth day of its illness, the baby was completely paralyzed. On the seventh day, 2 c.c. of serum was injected intraspinally. This was obtained from two children who had previously had the disease. Marked improvement resulted.

Ager⁵⁷ reports the death of two patients with afebrile, non-paralytic polioencephalitis, who were treated by autoinoculation with cerebrospinal fluid.

CHOREA AND TIC

Strauss⁵⁸ discusses the present conception of chorea. Heredity, neuropathic taint, fright and excitement have been frequently named as causes of chorea. Though these may play a rôle as predisposing causes, the exciting cause is probably of an infectious nature. The relation of chorea to rheumatism has been noted, and it has been suggested that the two diseases are caused by the same micro-organism. While from the blood of patients with arthritis diplococci are frequently isolated, the cultural and biological work that has been done on choreics has given conflicting results. At Mt. Sinai Hospital they had not been able to

54. Sawyer, W. A.: *Am. Jour. Trop. Dis. and Prev. Med.*, 1915, iii, 164.

55. Netter, Arnold: *Bull. de l'Acad. de méd.*, Paris, 1915, lxxiv, 403.

56. Alfaro, G. A., and Hitce, J. M.: *Semana méd.*, 1915, xxii, 211.

57. Ager, L. C.: *Arch. Pediat.*, 1915, xxxii, 755.

58. Strauss, I.: *Med. Rec.*, New York, 1915, lxxxviii, 255.

isolate organisms from the blood in chorea. Strauss thinks that the therapeutic test speaks against rheumatic arthritis and chorea being manifestations of one infection, since "In chorea one does not get the good results from salicylates as are obtained in polyarthritis."

The improvement following the use of arsenic suggests the possibility that a protozoon is the causative agent.

La Fetra reports that in two of his patients a streptococcus viridans was isolated from the blood.

Koplik believes that some organism is responsible, possibly not the streptococcus, but an organism associated with the streptococcus.

In an analysis of sixteen cases of chorea Middlemiss⁵⁹ calls attention to an underlying neurotic element, which, he thinks, has not received its due importance. In four of his series there was an undoubted history of rheumatism.

Mackenzie⁶⁰ reviews the various theories which have been given regarding chorea. He reports the detailed histories of sixty-four cases, and seems rather skeptical about any common origin for rheumatic arthritis and chorea.

Certain French observers having suggested a close relationship between chorea and syphilis; Comby⁶¹ determined the Wassermann reaction on 39 patients with chorea. Twenty-eight were negative, four were doubtful, seven were positive. Of these thirty-seven children, twenty-four gave positive tuberculin tests. This result would certainly not be interpreted as an indication of a tuberculous basis for chorea. Neither, according to Comby, do the positive Wassermann reactions in this series indicate an association with syphilis, both results being merely coincidences.

Koplik⁶² made a similar study on eleven successive cases of chorea. Eight patients gave a negative Wassermann reaction. In two patients the reaction was unsatisfactory, one was not done. If the study had been prolonged, positive Wassermann reactions might have occurred, for "a child affected with syphilis might contract chorea just as readily as another." Salvarsan has no virtues over previous remedies in the treatment of chorea.

Difficulty may be experienced in the elicitation of the reflexes in choreic patients. Swift⁶³ suggests that the examiner choose reflexes with long pendulums such as the knee and triceps, and that the test be preceded by instructing the child to hold still. Often a number of trials are necessary. Choreia may enforce, retard or add to the usual reflex.

59. Middlemiss, J. E.: *Edinburgh Med. Jour.*, 1915, xv, 333.

60. Mackenzie, I.: *Glasgow Med. Jour.*, 1915, lxxxiii, 259.

61. Comby, J.: *Arch. de méd. d. enfants*, 1915, xviii, 517.

62. Koplik, H.: *Arch. Pediat.*, 1915, xxxii, 561.

63. Swift, W. B.: *Albany Med. Ann.*, 1915, xxxvi, 425, 488.

Swift⁶⁴ notes a change in pitch and intensity during the prolonged sounding of certain vowels by patients with chorea. He has named this the voice sign. The patient is allowed to sit or stand with body relaxed. The patient is instructed to take a deep inspiration and sound for 15 to 20 seconds, the vowel *a* as in *are*. During the prolongation of this note contraction in the respiratory muscles may occur, changing the intensity of the sound.

An eosinophilia in the blood of patients with chorea is noted by Leopold.⁶⁵ He studied twenty cases, 50 per cent. of which gave an eosinophilia ranging from 4 to 16 per cent. In nine patients with recurrent chorea eosinophilia was found in six.

Acuna⁶⁶ obtained brilliant results in the treatment of chorea by the intraspinal injection of magnesium sulphate. He used a 25 per cent. solution, giving 1 c.c. of this solution for every 15 kg. weight. Exceptionally, the dose was increased to 1.25 or 1.5 c.c. per 15 kg. Improvement followed rapidly and seemed permanent. In each of the six cases reported, from one to four injections were given. In one patient, in whom 3 c.c. of the solution was used, there was a cessation of all choreic movements in forty-eight hours.

Passini⁶⁷ thinks that simple lumbar puncture is a useful therapeutic measure in chorea.

Vas⁶⁸ explains spasmus nutans in childhood as a "conditional reflex." This term was first elaborated by the physiologist, Pawlow, for the interpretation of certain physiologic phenomena, such as salivary secretion on thought of certain food. The practical bearing of this reflex to children was later studied by Krasnogorski and Czerny, and by Ibrahim. Blepharospasm following conjunctivitis and the holding breath spells seen in older children who have had tetany during infancy are examples of processes explained by this reflex.

Raudnitz had previously tried to show that the chief factor in the production of spasmus nutans was the dark dwelling house. When the child was put to sleep, its constantly repeated efforts to turn its head to a light area in the room produces the condition. Nystagmus occasionally followed, which seemed analagous to the nystagmus which develops in cave dwellers.

Such conditions, resulting from abnormal innervation, need not necessarily follow habitation in a dark room, according to Vas. They may also follow repeated efforts on the child's part to turn its head for hearing a certain sound, such as a clock, or to see a certain object, as

64. Swift, W. B.: *AM. JOUR. DIS. CHILD.*, 1914, viii, 279; 1915, ix, 132.

65. Leopold, S. S.: *New York Med. Jour.*, 1914, c, 225.

66. Acuna, M.: *Semana méd.*, 1914, xxi, 929.

67. Passini, F.: *Wien. klin. Wchnschr.*, 1914, xxvii, 1363.

68. Vas, J.: *Jahrb. f. Kinderh.*, 1915, lxxxi, 123.

a mirror. With repetition of the strain which the muscles of the neck undergo, abnormal innervations are produced, which develop into a pathologic conditional reflex. The nystagmus secondarily follows either by the tiring of the eye musculature or by the attempt of the eye to produce sharper pictures on the retina, which does not receive such if the head is being moved constantly. It has been shown in the dog that such movements may produce concomitant nystagmus.

The diagnosis and treatment of habit spasm is discussed by Grossman.⁶⁹ He states that the distinction between chorea and tic is easily made. "Movements in chorea are more irregular, incoordinated, and less rapid. The movements in tic are more regular, purposive, and repeated at intervals in just the same manner." Observation of these movements aggravates them in chorea, but lessens them in tic. Tic may affect any muscle or group of muscles. Blinking the eyelids is the most commonly observed. Such a tic may be accompanied by a facial grimace. Grossman gives the patient a tonic, prescribes a proper hygiene, but more important still is the reeducation of the patient. This is accomplished by proper breathing exercises, and muscular exercises which Grossman describes in detail.

Cockayne⁷⁰ reports what he terms "the jaw-winking phenomenon," in an infant. When the patient was a month old the right eyelid "went up and down" when the baby nursed. At six months there was a slight ptosis of the right upper lid. Cockayne thinks there must have been a defect of the motor path for the movement of the upper lid, at least, of that part above the nucleus of the third nerve.

SYPHILIS

Camp⁷¹ calls attention to the variety of manifestations exhibited in syphilitic infection of the central nervous system. Chronic encephalitis or meningo-encephalitis are the usual pathologic conditions found. He states that, "Syphilis as a cause of epilepsy is well known. A great many cases of idiopathic epilepsy are due to syphilis, and in a certain number of cases the syphilis is congenital." Mental deficiency is another of its manifestations.

Keyser⁷² reports a case of syphilitic hemiplegia in a child aged 5. The symptoms disappeared under antisyphilitic treatment.

Rohde⁷³ gives a detailed clinical and pathologic report of a case of syphilis of the brain.

69. Grossman, M.: *New York Med. Jour.*, 1915, cii, 339.

70. Cockayne, E. A.: *Brit. Jour. Child. Dis.*, 1914, xi, 352.

71. Camp, C. D.: *Am. Jour. Urol.*, 1915, xi, 233.

72. Keyser, T. J.: *Boston Med. and Surg. Jour.*, 1915, clxxii, 344.

73. Rohde, M.: *Monatschr. f. Psychiat. u. Neurol.*, 1914, xxxvi, 407.

Encephalitis of syphilitic origin may produce lesions not unlike those of an ordinary encephalitis according to Péhu and Gardière.⁷⁴ They report the sudden occurrence of hemiplegia in a two year old child, who had congenital syphilis. Death occurred in five days. Anatomically and histologically, the lesions could not have been distinguished from other forms of encephalitis. Large numbers of treponemata were found. The clinical diagnosis must depend upon the existence of syphilis in the parents or the occurrence of stigmata in the patient, or, finally, the action of mercury.

Zondek⁷⁵ observed a very puzzling case of apparent cerebral syphilis, which diagnosis the necropsy disproved. The patient was a well-developed and well-nourished infant, with a slight adenopathy, a palpable spleen and a weakly positive Wassermann reaction. During its stay in the hospital vomiting occurred, which was followed by the development of paresis and contractures on the left side. Despite the mercurial treatment the vomiting persisted, convulsions set in and general condition grew worse. Two subsequent Wassermann tests gave a three plus reaction. Lumbar puncture disclosed a clear fluid, under pressure, globulin positive, polymorphonuclear and mononuclear cells equal. The eye grounds showed a double neuroretinitis with a one-sided choked disk. Several weeks later the right side became spastic, and the child had tonic-clonic spasms, beginning on the left side, ending on the right side. Lumbar puncture was repeated. Lymphocytes predominated. Diphtheria and bronchopneumonia finally caused death. A diagnosis of hydrocephalus internus luetica with probable gumma was made. Necropsy showed no signs of syphilis (Aschoff). There was an extensive softening of the right frontal lobe, thrombosis of the longitudinal and transverse sinuses, and thrombosis of both Sylvian arteries; no endarteritis; external hydrocephalus.

The positive Wassermann reactions Zondek explains by an accumulation of lipoids in the blood stream from the broken down brain tissue. The choked disk is explained by increased intracranial pressure, the lymphocytosis by meningeal irritation.

Juvenile paresis is often overlooked in children, according to Leroux and Weinzweig.⁷⁶ A number are diagnosed as chronic meningoencephalitis. The somatic signs resemble those seen in the adult, namely, arrest of physical development and nondevelopment of the sexual organs. Children do not usually show the ideas of grandeur and persecution so common in the adult. A change in character and intelligence usually occurs. The child becomes taciturn and inattentive, loses his memory, and complains of headache and insomnia. Occasionally, the

74. Péhu et Gardière: *Arch. d. méd. d. enfants*, 1915, xviii, 330.

75. Zondek, H.: *Deutsch. med. Wchnschr.*, 1915, xli, 558.

76. Leroux, C., and Weinzweig, M.: *Arch. de méd. d. enfants*, 1915, xviii, 377.

beginning is abrupt, with epileptiform or apoplectiform attacks. Evolution is progressive without remissions. The average duration is from three to five years. The disease may be confused with idiocy, epilepsy, tumors or meningitis.

Schick,⁷⁷ Loffer,⁷⁸ Leonard,⁷⁹ Gostwyck,⁸⁰ Collett⁸¹ and others report cases of the disease observed in children.

Barkan⁸² discusses infantile and juvenile tabes, reporting twelve cases. Optic atrophy is usually the earliest symptom. Ninety-five per cent. present this symptom in childhood, in contrast to only 40 per cent. in the adult type of the disease.

The Wassermann reaction was positive in all. The patellar and Achilles reflexes were absent in 80 per cent. While in adults 80 per cent. exhibit a Romberg sign and ataxia, in children only 20 per cent. give these symptoms. Barkan says that a Romberg sign is rarely seen. Argyll Robertson pupils, and inequality of the pupils are usually present. The prognosis as regards sight is unfavorable, complete blindness being almost the rule. Mercury is of no avail.

EPILEPSY

Schlutz⁸³ says that a large number of infants have epilepsy. He makes some interesting observations in regard to its manifestations in childhood. The majority of cases develop it between the first and seventh years. The diagnosis of hysteria is frequently made when epilepsy is the disease present. The earlier epilepsy develops, the more unfavorable is the prognosis. Children seldom injure themselves during an epileptic attack. Very probably, these children have aura.

Turner⁸⁴ calls attention to the possible temporary remissions that occur in children at the age of 4 or 5, lasting until puberty. The treatment is very unsatisfactory.

Clarke⁸⁵ explains the pathogenesis of epilepsy on a Freudian basis. Epilepsy is essentially due to an arrest in the development of the psychosexual libido, he thinks. In this conception of epilepsy, the "fit" is explained as a libidinous outlet for the infantile unconscious, the nucleus of which is a desire on the part of the epileptic to return to a state of infancy. Close analysis of the epileptic supports this idea. The mental makeup of the epileptic resembles that of the child. They

77. Schick, B.: *Mitt. d. Gesellsch. f. inn. Med. u. Kinderh.*, 1914, xiii, 217.

78. Loffer, W. B.: *Cleveland Med. Jour.*, 1914, xiii, 607.

79. Leonard, E. F.: *Illinois Med. Jour.*, 1915, xxvii, 443.

80. Gostwyck, C. G. H.: *Jour. Ment. Sc.*, 1915, lxi, 254.

81. Collett, A.: *Jahrb. f. Kinderh.*, 1914, lxxix, 24.

82. Barkan, H.: *California State Jour. Med.*, 1914, xii, 488.

83. Schlutz, F. W.: *Journal-Lancet*, 1914, xxxiv, 504.

84. Turner, W. A.: *Brit. Med. Jour.*, 1914, ii, 665.

85. Clarke, L. P.: *New York Med. Jour.*, 1915, ci, 385, 442, 515, 567, 623.

memorize easily, while their constructive imagination is absent. In their speech, handwriting and deportment, they always show a childlike nature, never developing specific character individuality. An analysis of their dreams shows a similar condition. The dominance of the parents, the large number of simple repressed child wishes, and the functional character of the dream imagery is striking. The movements in the convulsion are very analagous to certain moods commonly seen in the infant, such as "the deflection of the head to the side, the quad-range mouth, etc." The prognosis is good in proportion to the possible development of the individual adolescent.

Shaw⁸⁶ states that the manifestations of epilepsy are due to a sudden "anemia of the cortex causing a discharge of the cortical nerve cells." This anemia is produced by sudden stasis and agglutination of the nucleoprotein coagulative elements of the blood in the cortical capillaries. The unusual tendency to agglutinate and the decreased alkalinity of the blood which is present in epilepsy makes this always possible.

Amesse⁸⁷ believes that chronic intestinal indigestion plays a great part in the production of epileptiform seizures. The obvious remedy is therefore dietary regulation.

Reed⁸⁸ has noticed that relief of constipation often cures epilepsy. He thinks that epilepsy is an infectious disease, the infecting agent being probably located in the intestinal tract and favored by mechanical constipation. Reed therefore proposed to remove the cause by performing an ileosigmoidoscopy followed by a colectomy, and reports favorable results.

Roentgenologic studies of the head, particularly of the sella turcica, in patients with epilepsy, were made by McKennan⁸⁹ and his co-workers. They found an overgrowth of the anterior and posterior clinoid processes, which are not only increased in area and length, but are folded over the pituitary gland. This bony overgrowth practically causes a local acromegaly.

Löwy⁹⁰ studied the blood during an epileptic seizure. He found, principally, a rise in the refractive index and a slight leukocytosis. Attacks of jacksonian epilepsy resulting from intracranial telangiectasis are reported by Sachs.⁹¹ The patients were each 10 years old. One showed a vascularity, involving chiefly the dura, the other the cortex. One of these patients presented telangiectasis of the face. In similar cases telangiectasis has been reported on other parts of the body.

86. Shaw, J. J. M.: *Jour. Ment. Sc.*, 1914, lx, 398.

87. Amesse, J. W.: *Colorado Med.*, 1914, xi, 424.

88. Reed, C. A. L.: *Jour. Am. Med. Assn.*, 1915, lxiv, 1047.

89. McKennan, T. M. T., Johnson, G. C., and Henninger, C. H.: *Pennsylvania Med. Jour.*, 1915, xviii, 429.

90. Löwy, J.: *Zentralbl. f. inn. Med.*, 1914, xxxv, 985.

91. Sachs, E.: *Am. Jour. Med. Sc.*, 1915, cl, 565.

The unsatisfactory results of treatment in epilepsy is indicated by the numerous measures recommended from year to year for its treatment.

Brodsky⁹² thinks that the bromids are the best drugs to use. However, the physical and dietetic treatment are of primary importance. Protein food should be reduced to a minimum and salt given only sparingly. Institutional treatment is most satisfactory.

Crotalin has given poor results according to Yawger,⁹³ while Jenkins and Pendleton⁹⁴ conclude that the number of convulsions are increased by its use, and in direct proportion to the amount used.

Held⁹⁵ noted a symptomatologic and pathologic similarity between epilepsy and rabies. He devised a serum prepared as follows:

"Blood serum and cerebrospinal fluid is gained from epileptics and passed through animals first properly prepared with rabific virus. The resultant is again conducted through a series of animals in order to attenuate unpleasant bodies." Using this serum, Held has obtained good results in the treatment of epilepsy. He deplores the use of bromids in this disease.

Kutzinsky,⁹⁶ Dubrowski⁹⁷ and Klotz⁹⁸ report favorably the results of the treatment of epilepsy with luminal (chemically, phenylethyl-barbituric acid). Klotz makes no claim for curing epilepsy, but notes that it decidedly diminishes the severity of the attacks and may affect their frequency. He uses a dose of from 0.05 gm. to 0.075 gm. in very young children, and from 0.1 gm. to 0.2 gm. in older children. This dose is given on two successive evenings, followed by two evenings of abstinence, to avoid cumulative effects. This alternation is continued.

Callosal puncture is suggested by Stieda⁹⁹ as a simple, safe and useful procedure in the treatment of epilepsy. In his experience, it was followed by at least temporary improvement. He recommends the procedure for other conditions when there is associated an increased intracranial pressure.

Many cases of epilepsy are due to reflex causes, according to Kalischer.¹⁰⁰ These causes may be present in the skin, bone or elsewhere. When such a cause is demonstrable, the removal of the

92. Brodsky, E. S.: *Med. Rec.*, New York, 1915, lxxxviii, 479.

93. Yawger, N. S.: *Pennsylvania Med. Jour.*, 1914, xvii, 964.

94. Jenkins, C. L., and Pendleton, A. S.: *Jour. Am. Med. Assn.*, 1914, lxiii, 1749.

95. Held, W.: *Chicago Med. Recorder*, 1915, xxxvii, 157, 342.

96. Kutzinsky, A.: *Monatsch. f. Psychiat. u. Neurol.*, 1914, xxvi, 174.

97. Dubrowski, W. G.: *Monatschr. f. Psychiat. u. Neurol.*, 1914, xxvi, 248.

98. Klotz, M.: *Therap. Monatsh.*, 1915, xxix, 129.

99. Stieda, A.: *Arch. f. klin. Chir.*, 1914, cv, 277.

100. Kalischer, S.: *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.*, 1914, xviii, 368.

peripheral irritation by operative measures may effect a cure. In children, in whom tetany is so frequent, the difficulty consists in distinguishing the two.

Surgical treatment of epilepsy, judging from the results, is unjustifiable, according to Minz.¹⁰¹

LITTLE'S DISEASE

Spiller¹⁰² studied the histories of four patients brought to him for spastic diplegia. Their ages ranged from 16 months to 3 years and 10 months. During infancy, these patients had all had jaundice, the duration of which varied from three days to three months. Several authors have noted in the adult a close relationship between diseases of the liver and alterations of the nerve cells of the brain. Spiller discusses this possibility in its application to Little's disease in childhood.

Throckmorton¹⁰³ reviews the various theories extant regarding this disease. He reports a case of early acquired spastic paraplegia, associated with various developmental anomalies. These were hypothyroidism, ichthyosis, and undescended left testicle. The presence of these conditions may be indicative of a degenerative condition which involves also the cells of the motor cortex or their neurons. Both paternal and maternal grandparents of this patient were cousins, wherefore Throckmorton observes that "consanguinity, even remote, may be a factor in the production of an inferior type or grade of human organism."

Batten and von Wyss¹⁰⁴ describe the atonic form of cerebral diplegia, of which they report four cases. Hypotonia of the extremities was marked, dorsiflexion of the feet on the legs and hyperextension of the legs was noted. The muscles responded normally to the faradic and galvanic current. There was no loss of sensation. If the patient was supported by the axillae, the thigh and legs became flexed at right angles with the body. Manipulation of the extremities in this position revealed spasticity. The mentality of these patients varied, deficiency being the usual finding. Three of these children were breech births. The condition may be distinguished from rachitic hypotonia by the absence of other rachitic signs, from amyotonia of Oppenheim by the electrical reactions.

Fearnside¹⁰⁵ reports a similar case.

Sharpe and Farrell¹⁰⁶ report striking results of cerebral spastic paralysis by subtemporal decompression. A history of difficult labor,

101. Korotnoff, N. I., and Minz, V. M.: *Russk. Vrach.*, 1914, xiii, Nos. 13 and 14, abstr., *Jour. Am. Med. Assn.*, 1914, lxiii, 616.

102. Spiller, W. G.: *Am. Jour. Med. Sc.*, 1915, cxlix, 345.

103. Throckmorton, T. B.: *Jour. Iowa State Med. Soc.*, 1915, v, 358.

104. Batten, F. E., and von Wyss, W. H.: *Brit. Jour. Child. Dis.*, 1915, xii, 65.

105. Fearnside, E. G.: *Brit. Jour. Child. Dis.*, 1915, xii, 166.

106. Sharpe, W., and Farrell, B. P.: *Jour. Am. Med. Assn.*, 1915, lxiv, 482.

and changes in the fundus, by ophthalmoscopic examination, are considered indications for operation. Sixty-five patients, selected from a total of 201, were thus treated by Sharpe and Farrell. Of these, thirty-four were diplegias, eleven were paraplegias, the remaining twenty were hemiplegias. Of these, six patients died, all within ten hours after the operation. Four of the six were under 2 years of age and "poor surgical risks." The usual pathologic findings are supracortical fibrous or cystic formation, the result of birth hemorrhages.

Resection of the posterior nerve roots is recommended by some and condemned by others in the treatment of Little's disease.

The compiled statistics gathered by Gümbe¹⁰⁷ are very disappointing. Schultless¹⁰⁸ notes that the hypertonicity may improve as a child grows older, and favors the postponement of operation. Bircher¹⁰⁹ recommends the operation. Blahd¹¹⁰ reports favorable results, having had but one death in ten patients so treated.

HYDROCEPHALUS

Dandy and Blackfan¹ divide internal hydrocephalus into two groups, recognizable clinically by the presence of phenolsulphonephthalein in the spinal canal after interventricular introduction. The patency of the communicating foramina is thereby determined.

In a normal individual phenolsulphonephthalein appears in the spinal fluid in from one to three minutes. It was also found that the dye so introduced will appear in the urine in from ten to twelve minutes and that from 12 to 20 per cent. will be excreted in two hours. If introduced into the subarachnoid space, in the normal individual it will appear in the urine in from six to eight minutes and from 35 to 60 per cent. will be excreted in two hours.

The excretion of phenolsulphonephthalein in the urine from the ventricles of patients with internal hydrocephalus of the obstructive type is prolonged. The appearance time is also delayed. The authors further state:

"In marked contrast to the negligible ventricular absorption was the high subarachnoid absorption. The appearance time in the urine and the duration of excretion following subarachnoid injections were normal."

In the type of hydrocephalus with patent communication between the ventricles and subarachnoid space there is a rapid appearance of the dye in the spinal fluid following intraventricular injection. However, "the absorption from the subarachnoid space of these patients is greatly

107. Gümbe¹, T.: Berl. klin. Wchnschr., 1914, li, 1353.

108. Schultless, M. W.: Rev. méd. de la Suisse romande, 1914, xxxiv, 550.

109. Bircher, M. E.: Rev. méd. de la Suisse romande, 1914, xxxiv, 550.

110. Blahd, E. M.: Lancet-Clinic, 1915, cxiii, 300.

diminished, amounting to about 10 per cent. in two hours. There is a corresponding increase in the time of first appearance of phenolsulphonophthalein in the urine and the time required for its total excretion from the subarachnoid space. The diminished subarachnoid absorption is the factor responsible for the production of the internal hydrocephalus."

The treatment of these two distinct types of hydrocephalus is obviously different. In the obstructive type surgical measures are necessary to relieve the obstruction. "In the communicating type the internal hydrocephalus is the result of diminished absorption from the subarachnoid space. At present the rational treatment would be to draw the fluid into other tissues where there is adequate absorption."

V. Bokay¹¹¹ again urges the use of Strasburger's illumination method in the determination of ventricular hydrops. Transparency is only present where the brain substance between the vault of the skull and the wall of the hemispheres is not more than 1 cm. thick. The position of the greatest amount of fluid and the thinnest part of the brain substance may thus be determined. V. Bokay recommends frequent lumbar puncture in the communicating type of hydrocephalus. In the obstructive type ventricular puncture must be done. These procedures may be repeated for a period of several years without danger. It should not be repeated oftener than every four or six weeks, nor should more than 50 c.c. be removed at one time. He reports an instance in which fifty-one punctures were done over a period of six and one-half years, followed by improvement.

Amenta¹¹² and Cannata¹¹³ performed Wassermann reactions on patients with hydrocephalus. Amenta found seven positive reactions in eleven patients. Cannata obtained ten positive reactions in nineteen patients. Sixteen of the mothers gave positive Wassermann reactions. He recommends antisyphilitic treatment.

Tyler¹¹⁴ and Oertel¹¹⁵ report cases of hydrocephalus.

Oden¹¹⁶ thinks that a contracted pelvis in the mother may be a possible cause for hydrocephalus developing after birth.

111. V. Bokay: *Jahrb. f. Kinderh.*, 1915, lxxxi, 17.

112. Amenta, F.: *LaPediatria*, 1914, xxii, No. 8, abstr., *Jour. Am. Med. Assn.*, 1914, lxiii, 1334.

113. Cannata, S.: *LaPediatria*, 1914, xxii, No. 10, abstr., *Jour. Am. Med. Assn.*, 1914, lxiii, 1888.

114. Tyler, G. T.: *Jour. S. Carolina Med. Assn.*, 1914, x, 682.

115. Oertel, H.: *Canad. Med. Assn. Jour.*, 1915, v, 653.

116. Oden, R. J. E.: *Jour. Am. Med. Assn.*, 1915, lxiv, 816.

MISCELLANEOUS

Talbot¹¹⁷ reports "the energy metabolism of an infant with congenital absence of the cerebral hemispheres." The patient was a large baby, weighing more than the average for its age. It was blind and apparently deaf. A decompression operation showed the cerebral hemispheres entirely absent, replaced by cerebrospinal fluid. The patient had a very low metabolism, as shown in Table 1.

TABLE 1.—J. J. M., INFANT WITH CONGENITAL ABSENCE OF CEREBRAL HEMISPHERES; METABOLISM EXPERIMENT

Subject	Body Weight Without Clothing, Kg.	Height, Cm.	Age	Periods	Heat Produced		Pulse Rate
					Per Kg. per 24 Hrs., Cal.	Per Sq. M. Body Surface, Cal.	
J. J. M.	8.48	78½	8 mos.	2	29	574	78
E. L. (normal) ..	7.58	71	8½ mos.	8	59	991	115
J. J. M.	7.45	..	9½ mos.	2	35	661	94
E. G. (normal) ..	9.37	74	10 mos.	5	51	907	106

Talbot's explanation for the low figures given are that the absence of volitional areas in the brain, the muscular underdevelopment, with the excessive development of fatty and bony tissues, coupled with the lack of muscular activity, made only a small number of heat units necessary.

Strauch¹¹⁸ reports a case of myatonia congenita of Oppenheim, presenting usual clinical features, "pseudo-paralysis of the muscles of the extremities and trunk with the exception of the diaphragm, and an involvement of the facial muscles." There was no response to the faradic and diminished response to the galvanic current. Skin and tendon reflexes were absent. Pathologic examination of the calf musculature was made. The muscle fibers appeared small. Areolar tissue was present in excessive amounts. Large numbers of sarcolemma nuclei and apparent karyokinetic figures indicated an effort at muscle regeneration.

Dunn¹¹⁹ records three cases of myatonia congenita with complete necropsy on one. The muscles showed marked atrophy with increased areolar tissue and connective tissue. Two well-defined tissue masses were seen in the sections of muscle. One seemed to be made up of

117. Talbot, F. B.: Arch. Pediat., 1915, xxxii, 452.

118. Strauch, A.: AM. JOUR. DIS. CHILD., 1914, viii, 298; *ibid.*, 1915, x, 16.

119. Dunn, C. H.: Boston Med. and Surg. Jour., 1914, clxxi, 191.

normal muscle fibers. The other was seen, under high power, to be composed of very small muscle fibers. Vacuolation of the large fibers was noted. Cortex, cerebellum, pons and medulla were normal. The changes in the cord were so slight that "they would have passed unnoticed in a routine examination."

Brauer and Schippers¹²⁰ report a case of myatonia congenita with clinical and pathologic findings not unlike those recorded by others.

Mott¹²¹ records a recovery following cerebral hemorrhage in a three year old girl. The hemorrhage was produced by a skull injury.

A case of myelitis of unknown origin is reported by Ashby.¹²²

Two cases of pseudohypertrophic muscular dystrophy, occurring in two boys of one family, are reported by Shaw.¹²³

Blauner¹²⁴ reports three cases of Friedrich's ataxia in one family. The first child developed the disease in its third year. Ataxia, explosive speech, characteristic carriage, and drunken gait were noted. The reflexes were present. The second child developed the disease in its fifth year. The third child developed the disease in its fourth year. All of these ended fatally.

Rothmann¹²⁵ reports a case of athetosis, with anatomical lesions in the corpus striatum, in a seven year old child.

Stamm¹²⁶ reports a case of multiple sclerosis in a boy of 12. The first symptom which occurred was blindness in one eye. Examination showed a central scotoma and a retrobulbar neuritis. The gait was spastic-ataxic. Oppenheim and Babinski reflexes were present. Clonus was positive. Later, the fundus examination showed a blurring of the temporal side of the disk. The Wassermann reaction was negative. The patient improved following the use of fibrolysin.

Griffith¹²⁷ describes the noteworthy features in a patient with acute cerebellar ataxia. The patient had a rapid recovery, one month after the onset of the disease.

Moreno¹²⁸ performed necropsies on forty newly born children. Examination of the brain disclosed a laceration of the tentorium in ten, with rupture of the falx cerebri in five. He was able to reproduce a similar condition experimentally in infant cadavers by exerting pressure on the sides of the head.

120. Brauer, B., and Schippers, J. C.: *Psychiat. en Neurol. Blad.*, 1914, Nos. 4 and 5, abstr., *Rev. neurol. and psychiat.*, 1915, xiii, 32.

121. Mott, W. W.: *Jour. Am. Med. Assn.*, 1914, lxiii, 1028.

122. Ashby, H. T.: *Brit. Jour. Child. Dis.*, 1915, xii, 142.

123. Shaw, F. B.: *Dublin Jour. Med. Sc.*, 1914, cxxxviii, 115.

124. Blauner, S. A.: *New York Med. Jour.*, 1914, c, 83.

125. Rothmann, M.: *Berl. klin. Wehnschr.*, 1915, li, 754.

126. Stamm, C.: *Arch. f. Kinderh.*, 1914, lxiii, 199.

127. Griffith, J. P. C.: *Am. Jour. Obst.*, 1915, lxxii, 549.

128. Moreno, S. F. M.: *Arch. mens. d'obst. et de gynec.*, Paris, 1915, iv, 145.

Sharpe¹²⁹ believes that spina bifida is caused "by the pressure exerted by an excessive secretion of cerebrospinal fluid, or what is more probable, some obstruction to its normal outflow." The preponderance of this anomaly in the lumbosacral region is explained on the basis that this point is the region of latest closure. The spinal cord and skin are both epiblastic tissues. The meninges and bones are mesoblastic tissues. In the third month of fetal life the adherent cord and skin are separated by the meningeal and bony structure of the canal becoming complete. The vertebrae of the dorsal region are the first to close, those of the lumbar region the last. The choroid plexuses are formed, however, in the second month of fetal life. Assuming that these may secrete an excessive amount before a proper closure occurs, and that undue pressure at this time may prevent such a closure, the mechanism of spina bifida is explained. Sharpe performed laminectomies experimentally and covered the defect with superficial sutures only. Large areas of skull were then removed and pressure applied to the head. This increased pressure caused protrusion of the meninges through the cleft.

PARALYSES UNCLASSIFIED

Fearnside¹³⁰ describes "a case of infantile hemiplegia affecting the left half of the body with considerable under development of the left upper extremity. Jacksonian convulsions affecting the paralyzed upper extremity, petit mal."

Wright¹³¹ and D'Espine¹³² report cases of infantile hemiplegia of obscure origin.

Erbsen¹³³ reports a case of bulbar paralysis of traumatic origin.

Bell's palsy occurring suddenly after fright is recorded by Synnott.¹³⁴

Platt¹³⁵ considers birth palsy the result of a primary plexus injury. In a certain proportion of cases, however, a shoulder joint or epiphyseal lesion may be present.

An unusual form of birth palsy is recorded by Gordon.¹³⁶ The condition was bilateral, symmetrical and identical in the two forearms. Two branches of the median and ulnar nerves supplying the flexor carpi radialis and flexor carpi ulnaris were apparently involved. The wrists remained extended in all movements of the forearm and arm, which were normal.

129. Sharpe, N.: *Ann. Surg.*, 1915, lxi, 151.

130. Fearnside, E. G.: *Brit. Jour. Child. Dis.*, 1915, xii, 136.

131. Wright, H. W.: *Jour. Am. Med. Assn.*, 1915, lxiv, 1577.

132. D'Espine, M.: *Rev. méd. de la Suisse romande*, 1915, xxxv, 52.

133. Erbsen, F.: *Monatsch. f. Kinderh.*, 1914, xiii, 254.

134. Synnott, M. J.: *Arch. Pediat.*, 1915, xxxii, 210.

135. Platt, H.: *Brit. Med. Jour.*, 1915, i, 793.

136. Gordon, A.: *Jour. Am. Med. Assn.*, 1914, lxiii, 2282.

Moren¹³⁷ discusses the differential diagnosis of paralysis in childhood.

BRAIN TUMOR

The unusual feature of a change in character as the primary sign of a brain tumor is presented by v. Malaisé.¹³⁸ Another patient showed the usual onset of headache and vomiting. A sarcoma was found in each instance.

An apparently complete recovery after operation for a cerebellar cyst is reported by Porter.¹³⁹

Salvini¹⁴⁰ removed an encephalocystocele and studied its structure. Other than twitching of the extremities due to irritation, the child appeared well after the operation. Whether this procedure will be the cause of a subsequent ataxia remains to be seen.

MENTAL DEFICIENCY

While the Binet-Simon method is still preferred in the measurement of mental capacity in childhood, numerous psychologists and neurologists maintain that its use, alone, creates false impressions in the determination of mental development.

Groszman¹⁴¹ condemns the habit of making quick examinations with the Binet scale. The determination of "exceptional development" is incomplete without a proper history, body measurements, thorough medical examination and the use of intelligence and physiopsychologic tests.

Potts¹⁴² discusses the methods "calculated to throw light upon the capacities of mental defectives for future work." In school, the child's aptness for manual work and for arithmetic should be observed. Various tests which may be of value are Warner's hand balance or an ataxiograph, where the subject holds a needle in holes of various sizes cut in a brass plate. All contacts made by the subject touching the plate are recorded by an electric battery connection.

The dynamometer measures the grip and also the dextrality, that is, the superiority of one hand over another. The use of the form board, and the cancellation of assigned symbols in a prepared form are also useful tests.

137. Moren, J. J.: *Kentucky Med. Jour.*, 1915, xiii, 92.

138. V. Malaisé: *München. med. Wchnschr.*, 1914, lxi, 1562.

139. Porter, L.: *Arch. Pediat.*, 1915, xxxii, 727.

140. Salvini, C.: *Ann. Surg.*, 1915, lxi, 10.

141. Groszman, M. P. E.: *New York Med. Jour.*, 1914, c, 1071.

142. Potts, W. A.: *Lancet*, London, 1915, clxxxix, 124.

Yerkes and Bridges¹⁴³ have devised a new scale for measuring mental capacity. Instead of using different scales for different mental capacities, a single scale is used, containing a series of tests applicable to children between 3 and 15 years. The subject is given a score in points, each question having a definite valuation. This serves as a basis for comparison with normal scores, and also makes possible a comparative appreciation of individuals which was not available by the Binet scale.

Belem and Lazar¹⁴⁴ introduce an additional method of testing mentality in the schoolchild—a test of speech function, particularly its grammatical expression. A series of questions are given. These are so worded that the answer necessitates the use of the various moods and tenses, as well as the comparative constructions of adjectives and adverbs.

Krause¹⁴⁵ urges the necessity of parental cooperation in the examination of mental defectives.

Hickson¹⁴⁶ examined 100 patients with mental deficiency at Vineland. All showed the reactions of spastic paralysis, indicating some organic brain lesion. The principal features are a lack of development on the affected side, a continuous Babinski reaction, irregularities in the Babinski and Oppenheim reflexes. Impairment of the lower facial branch is frequent. "It is rare to see an inmate of an institution for feeble-minded whistling," says Hickson. Contractures or hypertonicity of extremities are common. A lower blood pressure may be found on the affected side. In six necropsies done by Hickson at Vineland anomalies of other organs, such as hypoplasia of the cardiovascular system, supernumerary spleens and genito-urinary anomalies were noted.

Mendelsohn¹⁴⁷ reaches similar conclusions though his percentages are lower. Fifteen per cent. of his series showed evidences of infantile cerebral paralysis. In 6 per cent. of this group there is residual paralysis, function having been almost entirely restored. Paresis may be associated with epileptic convulsions or with choreiform movements and various tremors.

Dodd¹⁴⁸ believes that poor vision may prevent a child from receiving proper training and be productive of mental deficiency.

143. Yerkes, R. M., and Bridges, J. W.: *Boston Med. and Surg. Jour.*, 1914, clxxi, 857.

144. Belem, P., and Lazar, E.: *Ztschr. f. Kinderh.*, 1914, xii, 185.

145. Krause, J. T.: *Med. Rec.*, New York, 1914, lxxxvi, 337.

146. Hickson, W. J.: *Illinois Med. Jour.*, 1914, xxvi, 394.

147. Mendelsohn, J. J.: *Illinois Med. Jour.*, 1914, xxvi, 409.

148. Dodd, O.: *Illinois Med. Jour.*, 1914, xxvi, 404.

McCready¹⁴⁹ makes a plea for the application of mental hygiene in early childhood. "Early infancy is not too early to begin the inculcation of orderly habits of thought and action."

The care of the mentally backward child is discussed by Kendall,¹⁵⁰ Neustaedter,¹⁵¹ and Hebbard.¹⁵² The latter urges that a distinction be made between the "mentally defective dependent" and the "mentally deficient delinquent."

Kehoe¹⁵³ is frankly pessimistic regarding the care of the feeble-minded. He advises their custody, segregation and sterilization. Attempts at education he considers a waste of time and money.

Corwin¹⁵⁴ has seen mental improvement follow the removal of tonsils and adenoids.

Findlay¹⁵⁵ found a positive Wassermann reaction in 59 per cent. of fifteen mentally defective children. He recommends the use of neo-salvarsan.

Dendy¹⁵⁶ gives an enthusiastic account of Dr. Fernald's institutions at Waverly and Templeton. The keynote at these institutions is "occupation." Each individual is given work, that is pleasant and suited to his capacity. The boys first learn how to handle stones and wood, then tools. "From swinging a heavy mallet they pass on to hammering nails and using choppers and saws. No time is wasted trying to teach them to do what it is impossible for them to achieve."

Stevens¹⁵⁷ confirms the suggestion made by Sutherland regarding the association between syphilis and Mongolian idiocy. Stevens studied the blood and spinal fluid of these patients. Of twenty cases thus studied, he obtained 10 per cent. positive Wassermann reactions on the blood serum, 25 per cent. positive Wassermann reactions on the spinal fluid. The gold chlorid reactions showed color changes of two or more degrees, in 90 per cent. of the fluids. The globulin content of the spinal fluid was increased in 90 per cent.

Beier¹⁵⁸ discusses the various theories given for the causation of Mongolian idiocy. He states that an individual may present a Mongolian facial appearance and possess a normal mentality. In such individuals these Mongolian characteristics usually undergo change. The Mongolian idiot never changes in appearance. Treatment is unsatisfactory. Thyroid extract is useless.

149. McCready, E. B.: *Illinois Med. Jour.*, 1915, xxviii, 255.

150. Kendall, W. L.: *Oklahoma State Med. Jour.*, 1914, vii, 63.

151. Neustaedter, M.: *Am. Jour. Obst.*, 1915, lxxii, 520.

152. Hebbard, R. W.: *Albany Med. Ann.*, 1915, xxxvi, 19.

153. Kehoe, H. C.: *Illinois Med. Jour.*, 1914, xxvi, 407.

154. Corwin, A. M.: *Illinois Med. Jour.*, 1914, xxv, 400.

155. Findlay, L.: *Glasgow Med. Jour.*, 1914, lxxxii, 241.

156. Dendy, M.: *Jour. State Med.*, 1914, xxii, 412.

157. Coriat, I. H.: *Jour. Abnorm. Psychol.*, 1914, ix, 139.

158. Beier, A. L.: *Wisconsin Med. Jour.*, 1915, xiii, 348.

Coriat¹⁵⁹ reports explosive laughter and hydrocephalus as new symptoms in amaurotic idiocy.

Batten¹⁶⁰ describes a family of five children, non-Jewish, three of whom were affected with a progressive disease leading to dementia, blindness and paralysis. One of these showed changes in the macular regions of the eyes. The children became noisy, filthy in habits, and developed a spasticity of the extremities. All three died. In two of these a necropsy was done. In one no changes were observed in a histologic study of the central nervous system. In the other there was slight atrophy, with diffuse degenerative changes affecting the ganglion cells. The Wassermann reaction on the blood and spinal fluid was negative in both patients.

PSYCHIATRY

Hysteria in childhood is explained by the same mechanism as in the adult, according to Coriat.¹⁵⁷ He reports two cases in children, one manifesting itself by blindness, the other by convulsive attacks. A symbolic wish fulfillment formed the basis of both as shown by dream analysis. In the one case freedom from taking care of the younger members of the family represented the wish. In the other there was a typical Œdipus complex in the process of formation, a desire on the child's part to continue its relations with its mother.

D'Espine¹⁶² reports a case of astasia-abasia in a child 9 years old, due to hysteria. There was no evidence on examination of any organic lesion. The fundi were normal. The Wassermann reaction on the blood and spinal fluid was negative.

Strong¹⁶³ reports a case of hysterical paralysis in a child 2½ years old. During play in the physician's office, the condition entirely disappeared.

Stern¹⁶⁴ applies Freud's teachings to the explanation of pavor nocturnus.

Anxiety neurosis is discussed by Katz.¹⁶⁵ He reports five cases in girls ranging from 6 to 10 years. There was no past history of illness. The children became pale and weak, seemed tired and melancholic, and looked sick. There was loss of appetite. During play they would pause and either sit still dreaming, or would get up and run back and forth. After five or ten minutes they would resume their play. In two cases the girls seemed to have been frightened by details of war. In the other three the same story was elicited on subsequent interroga-

159. Coriat, I. H.: *Boston Med. and Surg. Jour.*, 1915, clxxiii, 20.

160. Batten, F. E.: *Quart. Jour. Med.*, 1914, vii, 444.

161. D'Espine, M.: *Rev. méd. de la Suisse romande*, 1914, xxxiv, 379.

162. Strong, M.: *West. Med. Rev.*, 1915, xx, 28.

163. Stern, A.: *New York Med. Jour.*, 1915, ci, 951.

164. Katz, O.: *Berl. klin. Wchnschr.*, 1914, li, 1835.

tion. Katz states that in children the cause of an anxiety neurosis is easier to ascertain than in the adult. Four of these patients had nervous parents, one was the child of a severe neurotic, a mother who had hallucinations.

Farnell¹⁶⁶ and Stier¹⁶⁷ discuss the psychopathic child.

Cordes¹⁶⁸ notes the rarity of psychoses in children and reports four cases.

Drysdale¹⁶⁹ reports a case of juvenile psychosis in a boy of 11 years. Psychopathic antecedents seems to be the strongest factor in the etiology of this condition. Anything which produces a mental or physical strain may be an exciting cause.

Rhein¹⁷⁰ reviews the literature on insanity in children and records several cases. The manic-depressive form is the most common variety seen.

Terman¹⁷¹ reviews the recent literature on juvenile suicides. In France 150 suicides a year is the record for those under sixteen years. In all other countries the situation seems to be growing worse. An analysis of the causes shows the school to be the greatest factor. Terman pleads for a "pedagogy founded equally on psychology, physiology and neurology."

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Wolfsohn, J. M.: *Arch. Int. Med.*, 1915, xvi, 257.

165. Farnell, F. J.: *Arch. Pediat.*, 1914, xxxi, 684.

166. Stier, E.: *Deutsch. med. Wchnschr.*, 1916, xli, 794.

167. Cordes, F.: *Kinder Arzt*, 1915, xxvi, 81.

168. Drysdale, H. H.: *Jour. Am. Med. Assn.*, 1914, lxiii, 1283.

169. Rhein, J. H. W.: *Am. Jour. Insan.*, 1915, lxxi, 471.

170. Terman, L. M.: *Jour. Abnorm. Psychol.*, 1914, ix, 61.

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CONGENITAL OBLITERATION OF THE BILE DUCTS

DIAGNOSIS AND SUGGESTIONS FOR TREATMENT *

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Congenital obliteration of the bile ducts is not an extremely rare disease. Over one hundred cases have now been reported. The reporting of further cases would be merely of statistical interest, were it not that certain misapprehensions in regard to this condition are current. These have come to my notice during a recent review of the literature upon this subject, and seem to warrant the reporting here of an additional case and further discussion of the condition.

REPORT OF CASE

Clinical History.—H. H., white, infant boy, was first seen when 7 weeks old in the Dispensary of the Harriet Lane Home. At this time the parents stated that the child's skin had been yellow since birth, that his eyes were yellow, and that the urine stained the napkin.

Family History.—Mother and father living and well, at 25 and 35, respectively. One other child 1 year old; no children dead; no miscarriages; no history of tuberculosis.

Past History.—Full term, natural birth; weight 8½ pounds at birth. No cyanosis or convulsions. Breast fed every three hours. First stools said to have been copious, loose and green, five to six daily. Icterus present since birth.

When first seen, Feb. 23, 1915, the child appeared to be a healthy and well-nourished infant, with an icteroid tint to his skin and sclerae, weight 10½ pounds, temperature 99 F. The pupils were normal. There were no signs suggestive of syphilis. The superficial glands were not enlarged. Heart and lungs normal. Liver enlarged. Spleen enlarged, projecting 2 cm. below the costal margin. A small hydrocele was present on the right side; genitalia otherwise normal. Circumference of abdomen 38 cm.

Stool: Specimen brought February 25 was semifformed, white and appeared greasy. Schmidt test negative for biliverdin, bilirubin and hydrobilirubin. Wasmann test negative. Liver palpable at 4.5 cm. below costal margin in mammary line.

The child's condition was unchanged when seen again on March 1. A specimen of stool brought for examination was white, but the mother stated that two movements on the preceding day had a yellowish tinge. A stool passed during examination had a distinct greenish tint, chemical reactions for bile and bile pigments negative.

* From the Harriet Lane Home and the Departments of Pediatrics and Pathology of the Johns Hopkins University.

On March 6 the jaundice had increased. The stools, four to six daily, contained no bile pigments. The circumference of the abdomen was 37.5 cm. The child gained in weight rapidly—9 ounces in ten days. There was no vomiting. Three days later the jaundice had increased; the temperature was 100.2 F. and the child had signs of bronchitis.

He was admitted to the Harriet Lane Hospital, March 9, a well-developed, well-nourished boy. Skin uniformly and deeply bile tinged; sclerae and mucous membranes showed a distinct but slight icteroid tint. No petechiae. No general glandular enlargement. When sleeping, the child breathed quietly; pulse rate 120. Liver and spleen palpable two finger breadths below costal margin. Slight signs of bronchitis were present. The examination otherwise was negative. The von Pirquet test was negative.

Blood showed 4,100,000 red cells, 14,500 white cells, small mononuclears 79 per cent., hemoglobin 80 per cent. (Sahli). Stool unformed, contained mucus and curds and had a slight but definite greenish-yellow tinge; biliary pigments lacking. Urine stained napkin yellowish green, was dark colored and acid, but not abnormal, save for the presence of bile. The temperature fell to normal after two days. The child was discharged on March 12.

The child's heel was punctured for a blood examination and there was great difficulty in stopping the flow of blood, the bleeding continuing for about eighteen hours.

On March 20 the child, aged 11 weeks, was taken by his mother to another hospital, and there a small incision was made in the back, for the collection of blood. The child bled from this incision until the evening of the next day. He was brought again to the Harriet Lane Home. Here he was given 10 c.c. of human serum, from his father, subcutaneously, and horse serum was applied directly to the wound. The hemorrhages were not checked until the morning of March 22, thirty-six hours later. A fine silk suture was introduced and the hemorrhage then ceased.

On March 24 the child vomited a small amount of blood-stained fluid and the next day the stool contained a large amount of tarry material mixed with fecal particles, and gave a positive guaiac reaction. The child was discharged on March 26. On March 31 he was brought back to the Home with a swelling upon one of the lower ribs, with surrounding ecchymosis. The stools contained blood occasionally. On April 9 another area of ecchymosis appeared on the left knee.

On April 13 the child ceased nursing well; he vomited after nursing and cried a great deal. The stools had been white since April 9. No evidence of blood had been seen. Numerous hemorrhages had appeared over his body. The child died on the afternoon of April 13. He was then 15 weeks old.

Postmortem Examination.—The following is an abstract of the necropsy protocol: Necropsy five hours after death. The body is that of a well-nourished and well-developed infant. The skin has everywhere a distinct citron hue. The sclerae and mucous membranes are deeply jaundiced. In numerous places over the body and extremities there are small, firm subcutaneous masses about the size of a pea; one of these is clearly the site of a sub-cutaneous hemorrhage.

The subcutaneous fat is well preserved. All the tissues are bile stained.

Save for yellow staining the heart and lungs are normal. The thymus is not enlarged; nor is the spleen. (Clinically, it had appeared to be definitely enlarged). The malpighian bodies of the spleen are very prominent. The kidneys are of normal size and appearance, but the cortex and fibrous tissues are stained a light yellow. The blood throughout the body is fluid. The stomach, small intestines, vermiform appendix, colon and rectum, all appear normal, except for deep-yellow staining of their substance. They contain only a little yellowish mucus and fecal matter.

The liver is deep purple, the surface and cut section are mottled by fine stellate radiations of connective tissue. The intrahepatic bile passages do not appear dilated.

Gallbladder and Biliary Passages.—The anatomical relations of the liver and adjacent organs seem quite normal, as also the lobulation of the liver. The gallbladder is represented by a fibrous cord with two dark, greenish-black enlargements that contain bile and thick mucus. The hepatic ducts are three in number—one to the left lobe, one to the anterior half and one to the posterior half of the right lobe—and meet in a common chamber. This chamber or globular dilatation of the common duct measures from 2 to 3 mm. in diameter. The three orifices of the hepatic duct are clearly seen and fine probes can be passed up each one even to the liver substance. A very fine duct leads upward from this chamber toward the nearest enlargement of the gallbladder tract and from this enlargement a fine lumen that admits a double platinum wire leads downward. An interval of 0.5 cm. remains without a demonstrable lumen. Distally from this last-mentioned enlargement a lumen is readily demonstrated and a fine probe passes through to the second enlargement. This ends blindly at about the position of the end of a gallbladder of normal size. From the chamber that receives the hepatic ducts a fibrous cord leads downward toward the duodenum. The papilla of Vater is present and of normal appearance. The pancreatic duct opens into it normally. There is a second small duct leading toward the fibrous cord just mentioned, but ending blindly at about 4 mm. distance. Beyond this the fibrous cord representing the common duct appears to be without lumen.

The pancreas is of normal size and appearance. The hepatic and pancreaticoduodenal arteries and the vena cava seem normal. The sympathetic plexus and the foramen of Winslow and its relations are normal.

The mesenteric glands are of normal size. On section they show a yellowish cortex, with a slimy, greenish-brown softened center. The glands about the head of the pancreas and the lesser curvature of the stomach are darker in color and larger. One such gland lies on each side of the hepatic vessels near the duodenum.

Microscopic Notes: Thymus highly cellular; cortical zone broad; central portion contains large and as a rule, well preserved Hassel's corpuscles; cell content of gland apparently normal. Lungs show nothing noteworthy. Spleen apparently normal; malpighian bodies prominent and show occasional germinal centers; the cells seem to be of normal character. Kidneys normal. Smaller mesenteric glands pale staining and rather lacking in cellular content, but otherwise normal; those from the lesser curvature of the stomach contain relatively few lymphoid cells and the septa and endothelial cells seem to have undergone partial solution. The cellular elements lie in a finely granular coagulum that is especially abundant just under the capsule of the gland. Sections from a gland at the root of the mesentery show changes of an intermediate character. Liver sections show quite marked biliary cirrhosis. The liver cells are of normal appearance, but not always well stained; their nuclei are well preserved. The capillary spaces between the columns of liver cells are large and well filled. The endothelioid cells lying in these are unusually well seen. They are not pigmented. Small collections of granular material that appears to be bile pigment lie here and there apparently free in the capillary spaces and between or upon the columns of liver cells. The cirrhotic areas contain small collections of lymphoid cells and delicate connective tissue cells. At the edges this tissue blends almost imperceptibly, through gradual transitions, into the normal liver parenchyma. The typical liver cells lie adjacent to others with progressively less protoplasm and less typical appearance until gradually they are lost among the mononuclear cells and young fibroblasts. Quite normal looking bile capillaries and ducts are seen in the cirrhotic areas and also large sinusoidal spaces filled with coagulated material that seems to be serum.

Serial sections were made of the biliary tract from the papilla of Vater to the gallbladder. These show pancreatic tissue of normal appearance and a normal pancreatic duct. The adjacent structures present no evidence of any inflammatory reaction. The usual position of the common duct is occupied

throughout almost its entire extent by loose connective tissue, in which lie the hepatic vessels and nerves. No lumen or definite strand of connective tissue representing the bile duct is found in this loose tissue. The ampulliform enlargement into which the hepatic ducts empty is seen to be lined in places with flattened epithelial cells; in other places the epithelium appears to have been rubbed off. The cystic duct is impervious through a short extent. Where patent, it is lined with elongated epithelial cells; where not patent, the lumen is occupied by a mass of these cells, those on opposing walls coming into contact. The gallbladder is deficient in epithelium in most sections. It appears to have been lined by flattened epithelial lining. Mucus is seen adherent to this. The wall seems deficient in mucous glands. The wall of the gallbladder, as that of the ampulliform enlargement, is formed of more or less tangentially arranged connective tissue cells. It is not unusually thick, and does not appear to be matted to adjacent structures. The usual blood vessels are present and are of normal appearance. The neighboring surfaces of the liver are covered with normal peritoneum.

Briefly, the conditions found were these: an anomalous arrangement of the hepatic ducts, absence of the common duct throughout the greater part of its extent, an impervious condition of the cystic duct with abnormalities of the gallbladder, and a moderate grade of cirrhosis of the liver.

ETIOLOGY OF CONGENITAL ATRESIAS OF THE BILIARY PASSAGES

The occurrences of such conditions as the above and the factors that lead to their production are better understood after a brief review of the embryological development of the parts. The process of development is quite complicated, and numerous abnormalities may result. These are, as a rule, not incompatible with life and indeed usually produce no symptoms whatever.

In the normal development of the embryo the early disk-like embryonic area that lies upon the yolk sac is gradually separated from it by infolding of its edges until it comes to form a more or less cylindrical cavity, the archenteron, or primitive gut, and the thickness of the body tissue of the embryo at each end becomes reduced to a thin membrane. When these membranes rupture the primitive gut unites with the structures beyond the membrane to form a continuous digestive tract.

In the early stages the embryo consists of two layers of tissue. Between these two layers, the outer and inner walls of the cylindrical embryo, develops a third layer, the mesoderm. With the formation of the primitive digestive canal, this mesodermic layer splits into two layers. The inner or splanchnic layer adheres to the archenteron and contributes to form its musculature and other structures, the outer or somatic layer adheres to the ectodermal layer and contributes to the formation of the body wall. The space within the mesodermal layer, formed by the splitting into two layers, is called the embryonic coelom, or body cavity. It is the forerunner of the pleural and peritoneal spaces.

As the veins from the yolk sac and adjacent structures pass into the embryo by way of the yolk stalk they traverse the splanchnic, or

inner layer of mesoderm which surrounds the archenteron and adjacent yolk stalk, and then pass forward in it toward the heart, which, it will be remembered, lies at this stage of development far anteriorly, or in the cervical region, not until later descending to its future position. These veins, one on each side of the gut, soon become so large that they bulge out the splanchnic mesoderm, in which they lie, and bring it into contact with the opposing parietal wall. Fusing along the lines of contact, these two layers form a thick semilunar fold which projects horizontally into the coelom, or body cavity, from the ventral wall of the body. Its dorsal edge is continuous in the median line, with the mesoderm surrounding the digestive tract in that portion that is to become the duodenum. This fold is known as the septum transversum. Its later position is indicated by the position of the diaphragm, liver and pancreas. It is in this fold that the liver, pancreas and biliary passages later develop.

The liver makes its appearance later, when the embryo has attained a length of about 3 mm., at $2\frac{1}{2}$ to 3 weeks. The first indication of it is a longitudinal groove in the ventral surfaces of the archenteron just below the stomach. The endodermal cells lining the anterior portion of the groove rapidly proliferate and form a solid mass of cells which projects ventrally into the septum transversum. This solid mass of cells is the beginning of the liver proper. It comes to consist of solid columns of cells and columns with a central core or lumen. The former represent the liver parenchyma, the latter the bile capillaries and biliary passages. Numerous sinusoidal blood vessels penetrate it and subdivide it into liver lobules and trabeculae.

The lower or distal portion of the groove remains hollow and represents the future gallbladder. Constrictions appear between the intestines and the developing hepatic and cystic structures and gradually separate them from the intestine until they are connected with it only by a stalk, that intermediate portion of the groove which forms the ductus choledochus or common duct. The ductus choledochus is at first wide and short, in embryos of 5 to 8 mm. in length. It later elongates and becomes more slender. The developing gallbladder is constricted off from it, the constricted portion of the lumen forming a cystic duct. The hepatic ducts developing in the liver cell mass open into this ductus choledochus.

The beginnings of the pancreas appear a little later than those of the liver. While the ductus choledochus is still short and broad, there appear two cellular outgrowths, one on each side of the proximal end of the duct. That on the left side soon degenerates and disappears completely; that on the right side continues to develop and forms the ventral pancreas. At the same time an outgrowth appears on the dorsal surface of the intestine, the duodenum, and develops into the dorsal pancreas. The two are for a time separated by the portal vein, but they grow around this, and coming into contact, fuse intimately, the ventral pancreas becoming the head of the completed organ. There are at

first two principal ducts, that of the ventral outgrowth, now the head, the duct of Wirsung, opening into the ductus choledochus, and that of the dorsal outgrowth, the duct of Santorini, opening into the duodenum on its dorsal surface. After the fusion of the two portions of the gland occurs, anastomoses form between the branches of the two ducts and the proximal portion of the duct of Santorini usually degenerates. When the closure of the duct Santorini is complete, the secretion of the entire gland empties into the ductus choledochus through the duct of Wirsung.

It is seen that the formation of the biliary passages is a complicated process and one presumably lending itself readily to the formation of abnormalities.

Types of Abnormalities Found.—Minor abnormalities, especially those affecting the cystic duct alone, occur with great frequency. I have recently found complete occlusion (atresia) of the cystic duct as the only abnormality in two instances, in three consecutive post-mortem examinations of infants and young children. The gallbladders in these cases were normally formed and contained clear, colorless, mucoid material. Variations in the number and arrangement of the hepatic ducts are not uncommon.

The relations of the gallbladder to the liver vary greatly in individual cases. It is often almost completely enclosed in liver tissue, but sometimes it is almost free. It may even be entirely free from the liver and suspended from it by a mesentery, or hanging from it by the ductus cysticus as a stalk. In rare cases the gallbladder is placed on the posterior surface of the liver; in such cases other abnormalities in the biliary passages are present.

The ductus choledochus may be found double, as may the ductus cysticus, and the ducts may open into it in various abnormal ways. An independent hepatocystic duct may lead from the liver directly into the gallbladder¹ (Wrightman²). Unusual weakness of the walls of the common duct or blocking of the lumen at some stage may cause enormous dilatation of the duct, idiopathic choledochus cyst. The obstruction need not be a permanent one (Weiss³), but may permit the passage of bile at times.

The relative size of the different ducts may vary greatly. Occasionally the constriction amounts to atresia or complete obliteration of the gallbladder (Benecke,⁴ Flebbe⁵), or of one of the biliary ducts.

1. This condition exists regularly in various animals (Quain and Symington: Quain's Anatomy, iii, Pt. 4, p. 128).

2. Wrightman: Accessory Cystic Duct; Report of a Case, West. Med. Rev., 1915, xx, 234.

3. Weiss: Ein seltner Fall von systcher Erweiterung des Ductus choledochus, Berl. klin. Wchnschr., 1909, xlvii, 1843.

4. Benecke, Rudolf: Die Entstehung der kongenitalen Atresie der grossen Gallengänge, nebst Bemerkungen über den Begriff der Abschnürung. Universität's Programm., Marburg, 1907.

5. Flebbe: Ueber angeblichen Obliteration des grossen Gallenwege, Inaug. Diss., München, 1907, cited by Aschoff and Elperin.

Thomson⁶ in 1890 collected and carefully tabulated forty-nine cases from the literature and added a case of his own. His article was accompanied by an excellent drawing of his specimen and also by diagrams showing the extent of the abnormality present in these cases from the literature in which this could be determined from the descriptions at hand. Benecke⁴ extended this list in 1907 to seventy-four cases of congenital atresia of the biliary passage. Since then about forty additional cases have been recorded.

Thomson represented diagrammatically the conditions found in thirty of the fifty cases collected by him. He arranged "in a sort of order of sequence diagrammatic representations, on a small scale, of the exact conditions of the gallbladder, cystic, hepatic and common ducts, and the duodenum, as described by the writers in a majority of the published cases." Where a part of the apparatus, such as the gallbladder, cystic duct, etc., was not mentioned in the description, he represented it as normal. He stated that the main points "will be found to be fairly and accurately represented in the table, so far as they can be ascertained."

I have reproduced these thirty drawings and added others, showing in like manner the conditions found in other cases⁷ (Figs. 1 to 4).

As is seen from these diagrams, the lesions found are of the greatest variety. Clinically, those cases involving the common ducts, or more rarely the hepatic ducts, are of importance. The published cases are usually of the former type, and thus the impression has come to prevail among clinicians that the common bile duct is most frequently affected in congenital atresia. This is rendered at least doubtful by the frequency with which impervious cystic ducts are found postmortem, both in children and adults (Benecke).

When the common duct is affected, there may be stenosis or atresia at any point in its course, or the duct may be represented merely by a fibrous cord, or it may be absent altogether. In about one half of such cases other lesions are associated with the lesion in the common duct—commonly an impervious cystic duct or malformations of the hepatic ducts, or both. The atresia may also involve the pancreatic duct. *In over 16 per cent. of all reported cases of atresia of the bile ducts, both the cystic and the hepatic ducts are essentially normal and communicate with each other.*

Factors in the Production of the Abnormalities.—There have been three main theories as to the cause of congenital atresias of the bile

6. Thomson, J.: On Congenital Obliteration of the Bile Ducts, Edinburgh Med. Jour, 1892, xxxvii, 606.

7. Where like conditions were found in two or more cases, one diagram is used to illustrate all. When a given case differed in some unimportant detail, the fact is indicated by placing the name of that case in parenthesis.

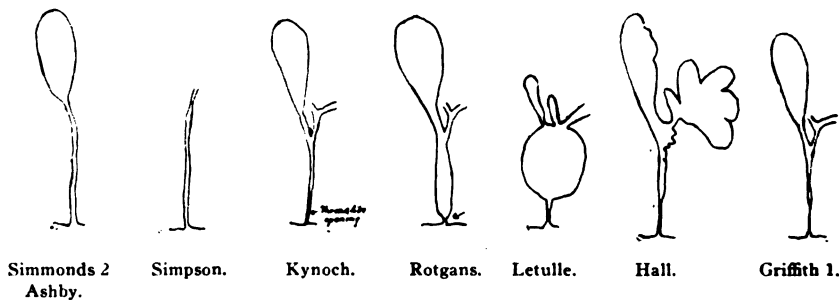
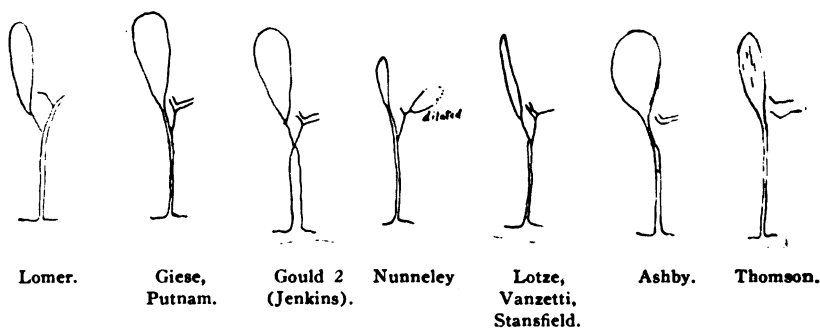
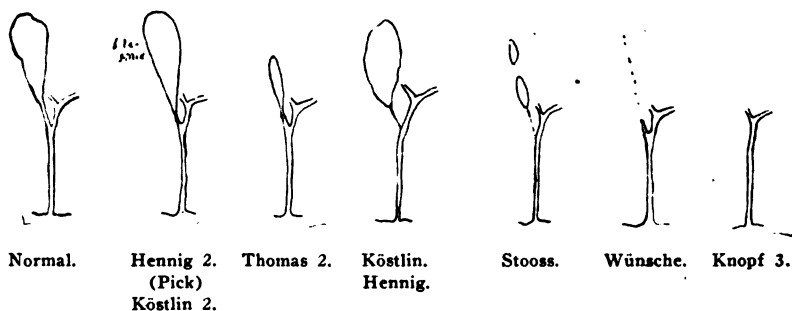


Fig. 1.—Diagrammatic representations of the conditions present in the recorded cases of congenital obliteration (atresia) of the bile ducts.

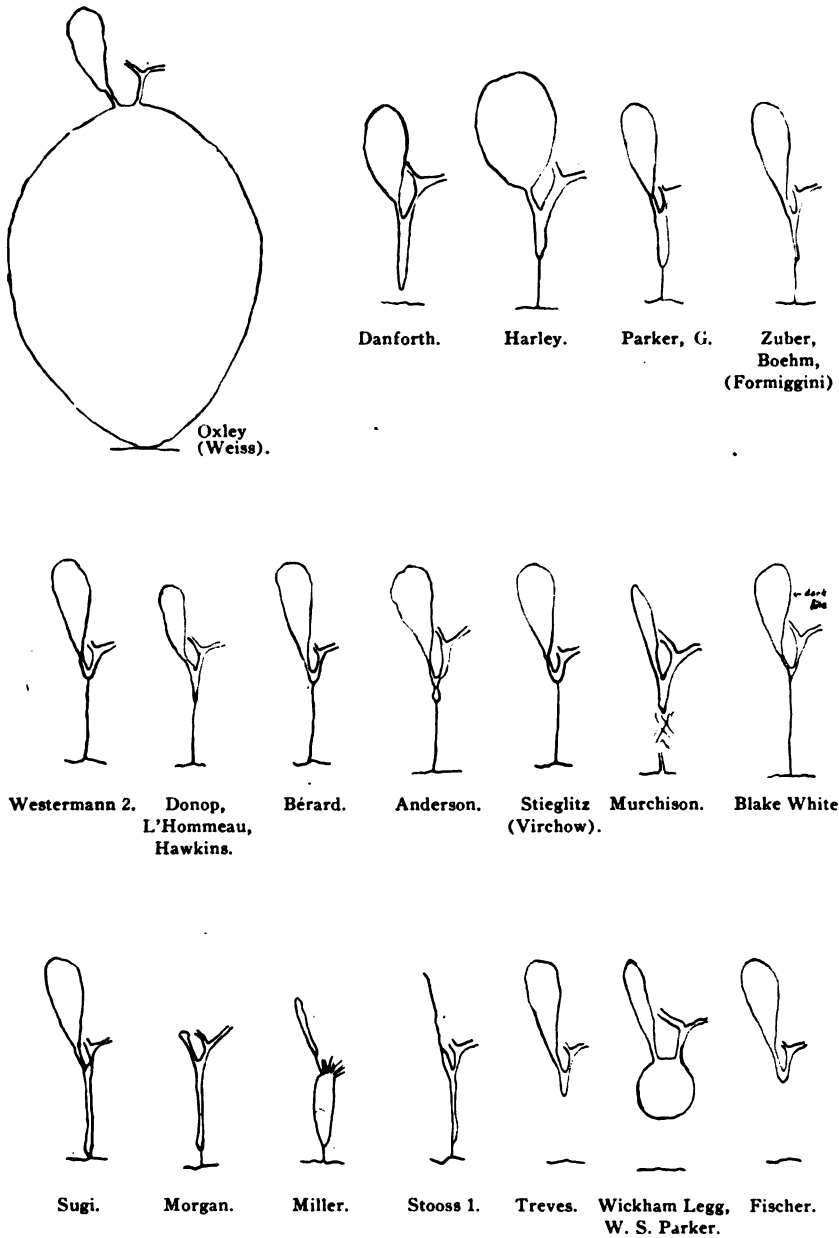


Fig. 2.—Diagrammatic representations of the conditions present in the recorded cases of congenital obliteration (atresia) of the bile ducts.

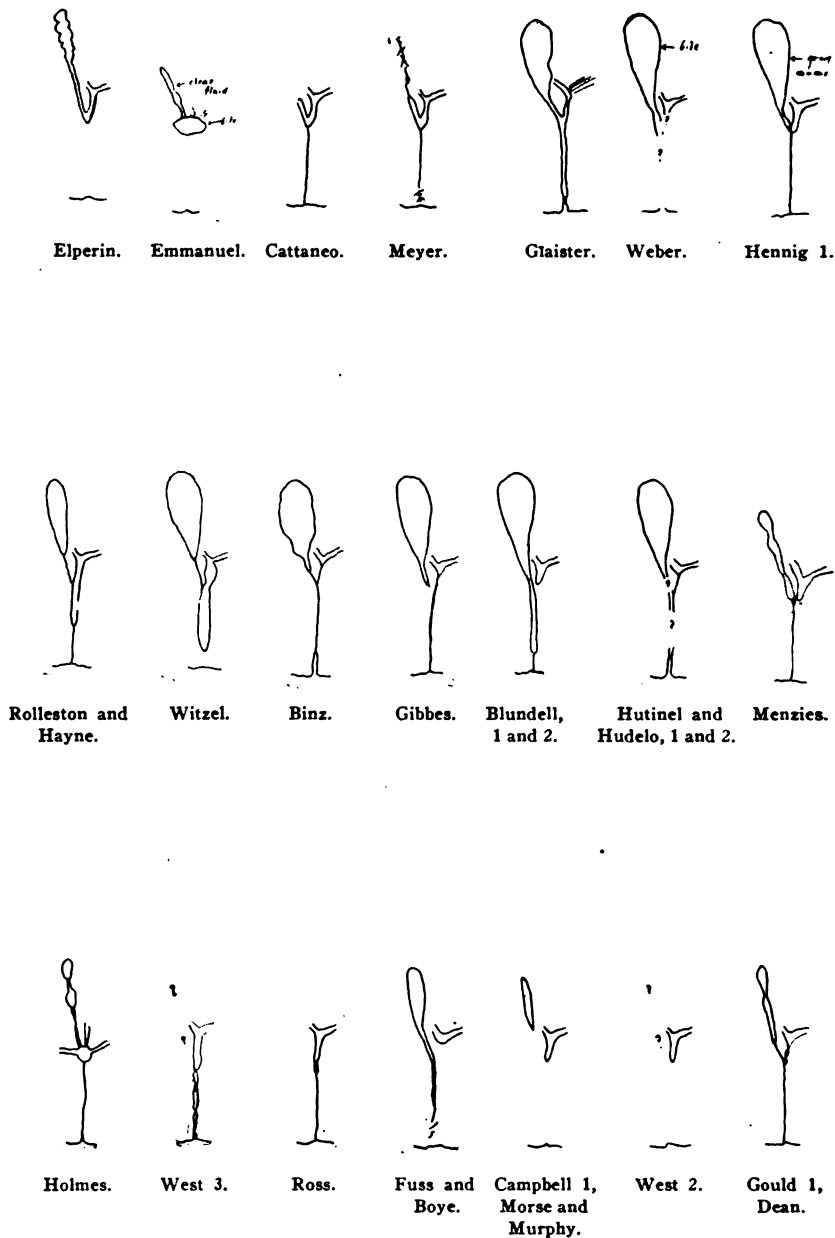


Fig. 3.—Diagrammatic representations of the conditions present in the recorded cases of congenital obliteration (atresia) of the bile ducts.

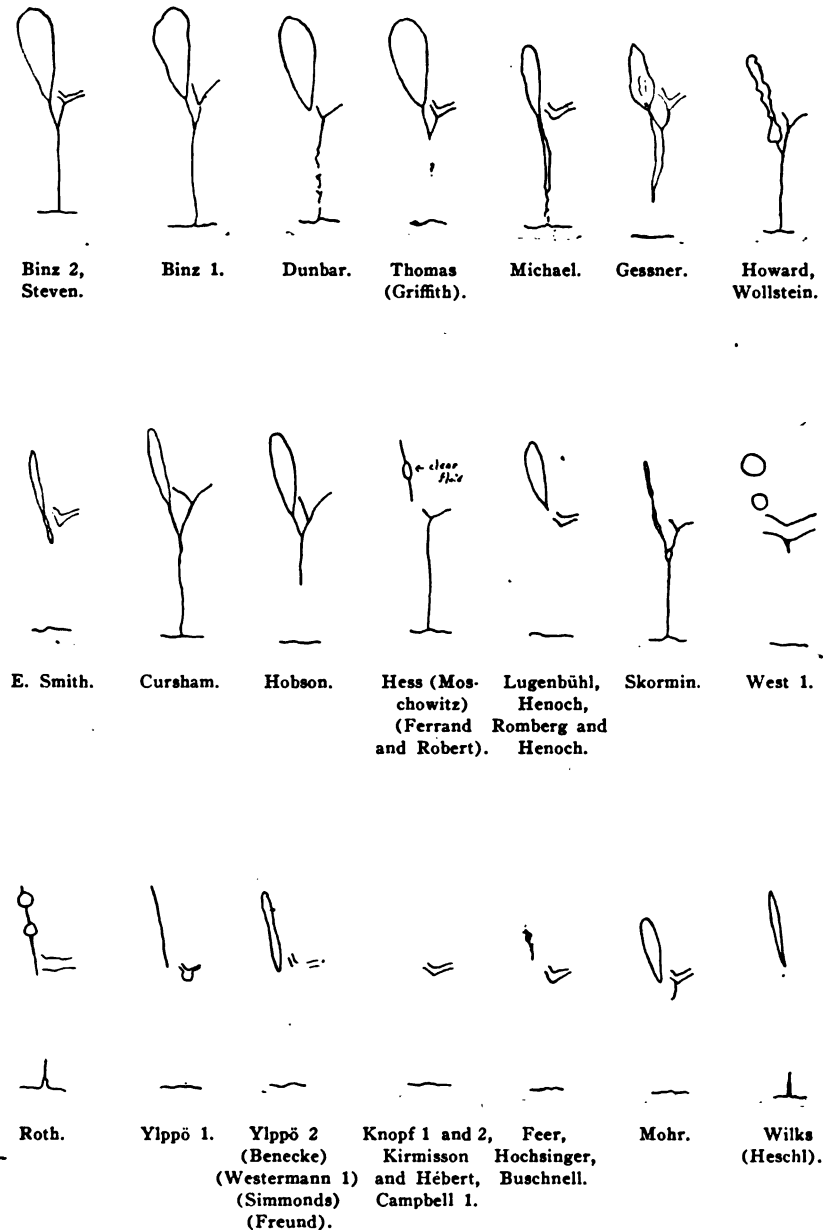


Fig. 4.—Diagrammatic representations of the conditions present in the recorded cases of congenital obliteration (atresia) of the bile ducts.

ducts: (1) that the condition is due to congenital syphilis; (2) that the majority of the cases, if not all, are examples of congenital malformation; (3) that they are the result of fetal peritonitis. A fourth theory has been suggested, rather than definitely advanced: (4) that the condition is the result of a catarrhal process within the ducts themselves.

That the condition is not due to congenital syphilis has been definitely decided. Thomson showed that syphilis is usually absent. Benecke came to the same conclusion. In recent cases the Wassermann reaction has been negative.

Thomson concluded in 1892 that the lesion is, in the great majority of cases, merely a congenital malformation. It may be a narrowing, and not atresia. He found that the situation of the lesion "varies almost indefinitely," there being "examples of almost every conceivable variety." When the lesion consists at first merely of a narrowing of the passage, the interference caused by this might produce catarrh, blocking of the passage, and finally obliteration, the obliterated portion persisting as a fibrous cord or disappearing entirely. This obliteration he felt was usually complete in early intra-uterine life. It might, however, occur at variable periods, and occasionally was not complete till after birth. The condition was regarded by him as a progressive one, becoming more extensive the longer the patient lived. When the passage of the bile becomes obstructed, biliary cirrhosis of the liver ensues, and with increasing interference with the functions of the liver come the usual symptoms of vomiting, hemorrhage, convulsions, diminished vitality, and finally death. The inflammatory process, Thomson said, might spread to the adjacent peritoneum. Evidences of peritonitis seemed to him in some cases "certainly secondary to the malformation of the ducts," and probably always secondary. In the usual sharp limitation of the lesion to the gallbladder and its ducts, with the escape of neighboring structures, and in the absence, in most cases, of traces of past peritonitis elsewhere in the abdomen, he found "strong reasons" for thinking that peritonitis is not the cause of congenital atresia of the bile ducts.

Benecke, in tabulating the lesions present in the seventy-four cases recorded by him, found that the constriction or atresia occurred at the level of the papilla of Vater in the great majority of cases. He accepted the view that the ductus choledochus is at no stage of its development a solid core that might fail of perforation, but always an open fold of the duodenum. In the fact that the liver, a part of the same primitive tissue, is always present in cases of congenital obliteration of the bile ducts, he found proof that the condition is not always agenesis. His tabulation seemed to indicate that the constriction of the primarily patent duct occurs at the duodenal end, that is, in the papilla of Vater, in the vast majority of cases, however much farther it might afterwards extend up the tract.

To explain this, he developed the theory of an *Abschnurungsprozess*. By *Abschnurung* we may understand a tying off, a twisting or a blocking of an otherwise normally formed duct. Such an *Abschnurungsprozess* might be due to simple traction of the mesentery or of bands of mesentery. The rapid growth of the adjacent and relatively enormous liver might readily produce such traction on the mesenteric attachments as would constrict or twist the ductus choledochus at its duodenal outlet, tying it off as it were;⁸ or ingrowing (intercalating, *interkalierende*) duodenal epithelium might so overgrow as to block the tube, as might the epithelium of the duodenal end of the duct itself; or, inflammatory processes radiating from the liver outward might do so. These are the grosser, more mechanical forms of *Abschnurung* suggested by Benecke.

The term *Abschnurungsprozess*, as used by Benecke, has a less precise meaning, however, and one that leads into the realm of normal development. It is used for any process of constriction. The separation of the embryo from the yolk sac becomes an *Abschnurungsprozess*. So, also, is the separation of the liver, the lungs, the thyroid, the thymus, or Hassel's corpuscles, from the adjacent tissues. It is only when such constrictions occur at unusual times and places, or to unusual degrees, that they become pathologic. The normal formation of the liver and gallbladder is a typical *Abschnurungsprozess*. The intestinal canal forms a fold which rises up more and more as a sac; on the summit of this sac, the specific liver cells develop. The liver develops rapidly; the neck of the sac remains passive or nearly so, and the ductus choledochus is formed. There is in the portion of the tract that is to form the ductus choledochus an inherent *Wachstumsschwäche*. If this is accentuated (!) there occurs a *vollkommene Stehenbleiben*, a *totale Abschnurung*.

8. The recent studies of Engel (Nuove ricerche sui vasi biliari aberranti, Ricerche n. lab. di anat. norm. d. r. Univ. di Roma, 1909-10, xv, 135-283, Pl. 4) upon the origin of the vasi biliari aberranti and so-called mucous glands of the liver emphasize the effect of pressure from adjacent organs upon the developing liver. He has shown that the relatively simple form of the early embryonic liver undergoes considerable modification through what is apparently pressure atrophy of previously formed parenchyma and resultant sclerosis. Fissures may be thus formed and previously existing fissures accentuated. The bile ducts in the regions thus modified may disappear or remain as blindly terminating sacs, the so-called vasi biliari aberranti or appendices, or, if occluded lower in their course, may give rise to racemose glandlike structures, the so-called biliary mucous glands.

To such processes Engel attributes the differences in the form of the liver in different animals. As a rule the development of the stomach and other organs on the left side lead to the relative diminution of the left lobe. In the horse the right lobe loses its earlier volumetric predominance over the left lobe because of the enormous development of the colon in this animal. Furthermore, the change occurs in postnatal life.

The number and location of the vasi biliari aberranti and related structures varies in a measure with the extent of the gross modification.

The two points of especial interest here are, first, that the process should result in atrophy, localized atresia and other changes in the biliary tract, and second that the cause of these changes should exert this influence at any time during later fetal life—and even extend into extra-utrine life.

Benecke's theory is far from being clear, and really involves two different conceptions. It offers little help in explaining congenital atresia of the bile ducts. As is shown by the diagrams, the constriction, or atresia, does not occur in the terminal portion of the ductus choledochus so frequently as Benecke thought, and he is mistaken in thinking that the papillary portion is always involved, even in those cases where the lesion is in the lower half of the duct. Thomson's earlier view, that the constriction does not occur uniformly at any definite point, finds increasing support as additional cases are recorded.

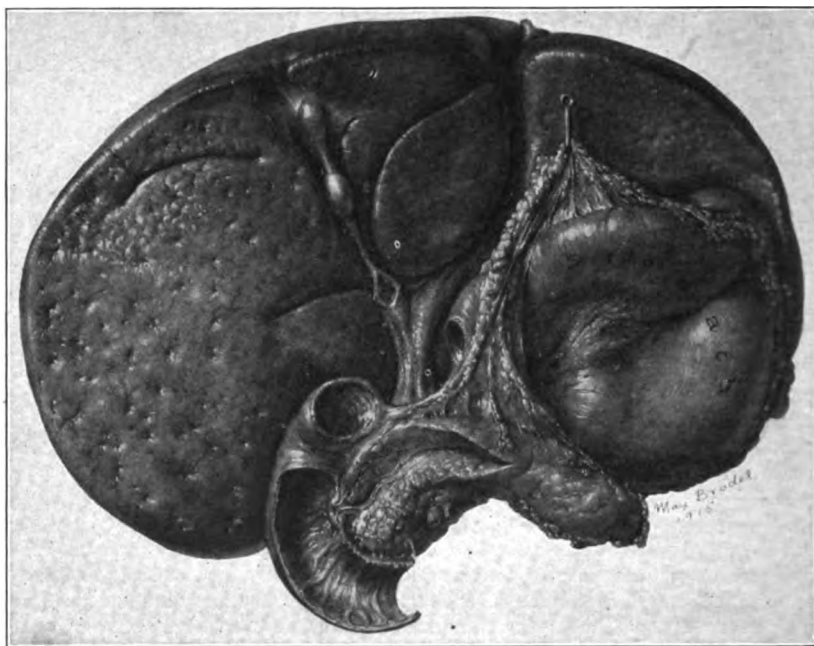


Fig. 5.—Liver viewed from below, showing region of gallbladder and extrahepatic ducts. Below the duodenum is shown in section through the papilla of Vater and the opening of the bile and pancreatic ducts. Note the cirrhosis.

Ylppö,⁹ in a recent report of two cases of congenital atresia of the bile ducts, states that the extrahepatic ducts are first patent and then lose their lumina through proliferation of their epithelium, becoming solid cords, only later becoming patent again. In this he quotes Böhm, who found the etiology of biliary atresia in "einen Persistenz der fötalen physiologischen Epithelokklusion in Analogie zum gleichen Prozess im Darm (Tandler, Forssner)." Such a developmental history, if correct, accounts better than that given above for the variety of locations in which atresia is found.

9. Ylppö: *Ztschr. f. Kinderh., Orig.*, 1913, ix, 317.

Fetal Peritonitis.—It seems hardly necessary to presuppose the existence of any inflammatory process during intra-uterine life to explain the occurrence of these atresias. It may be said that atresias of greater or less extent are relatively common malformations in the tubular structures of the human embryo; those of the esophagus, rectum, urethra and vagina may be cited. Constrictions and degenerations of greater or less degree are, as has been seen, an essential part of the formation of the normal biliary and pancreatic structures. Cohesion and fusion of fetal tissues is a common occurrence when for any cause they are brought into intimate contact. Examples of these have been given above in describing the formation of the septum transversum and the pancreas. Numbers of examples might be cited. In doing routine necropsies on infants it is not uncommon to find the lobes of the lungs more or less bound to each other by delicate adhesions, or to find the pleural cavity partially obliterated, or the spleen adherent to the adjacent parietal wall. The lack of mesentery on portions of the large gut is an example of this tendency to coherence. At first hanging freely and almost completely clothed with membrane, the peritoneum later comes into close contact with the body walls and loses much of its peritoneal coat through fusion. The extent of this fusion or coherence between fetal tissues coming into close contact varies greatly in different individuals, as postmortem study of infants shows. To speak of the process as fetal peritonitis or pleuritis is misleading, as it is probably unrelated to the conditions usually designated as peritonitis and pleuritis in later life.

Rolleston and Hayne's View.—Rolleston¹⁰ has ardently supported the view that cirrhosis of the liver is the primary condition and that the lesions in the bile ducts are secondary to it. As the cause of the cirrhosis he postulated some poison being excreted by the liver and setting up in that organ a cholangitis that subsequently descends to the larger bile ducts and there leads later to organization. The process is clearly not syphilitic in character, and it is not known what it may be.

Rolleston approached the question from the viewpoint of pathology of the liver in adults. He was impressed with the "almost constant" occurrences of cirrhosis in cases of congenital obstruction of the bile ducts as compared with the infrequency and irregularity with which cirrhosis follows obstruction of the larger bile ducts in later life; and also with the large size of the liver in congenital cases and its resemblance in this respect to the liver of hypertrophic biliary cirrhosis

10. Rolleston and Hayne: Brit. Med. Jour., 1901, i, 758.

This theory lacks satisfactory support. Cirrhosis of the liver in adults consequent upon biliary obstruction apparently does frequently occur. Mangelsdorff¹¹ (1882) and Ford¹² (1901) have collected over two hundred cases of this condition. The obstruction in most of the cases was calculus or carcinoma of the head of the pancreas. As described by Ford, the livers in these cases of obstructive jaundice are "greatly enlarged with a rough jaundiced surface and considerable perihepatitis;" the cirrhosis may be "interlobular, intralobular, or pericellular in type."

Doubtless in these cases and in the congenital cases it is possible to have, as in practically every other hypertrophic cirrhosis of the liver, a decrease in size of the organ, if the patient lives long enough, though the patients with congenital conditions of that kind seldom live long enough. Moreover, in certain cases of congenital obstruction in which death has occurred soon after birth, cirrhosis of the liver has been wanting or has not been conspicuous.

Thus there is evidence that both in adults and in children (Ford) biliary stasis has resulted in the same sequence of events and in the same pathologic findings in the liver as are found in cases of congenital obstruction of the bile ducts.¹³

A Composite View.—It would seem that the cause of congenital atresia of the bile ducts must be sought, as a rule, in a faulty development from the primary tissues. What the causes of this are we scarcely know. They are doubtless the same as those operative in the production of atresias in other tubular structures.

11. Mangelsdorff: Deutsch. Arch. f. klin. Med., 1882, xxxi, 522, cited from Ford.

12. Ford, W. W.: Obstructive Biliary Cirrhosis, Am. Jour. Med. Sc., 1901, cxxi, 60.

13. The experimental work of Beloussow (1881), Camalis (1886), Lahousse (1887), Pick (1890), Gerhardt (1892), Lannaq (1897), and Harley (1898) shows that in experimental obstruction in animals the same changes in the liver may be found as in cases of biliary obstruction in human beings. Vaughn Harley (Brit. Med. Jour., 1898, ii, 1743) studied the conditions in cats. The animals were operated on under ether with strict aseptic precautions. The left hepatic duct was ligated, the other ducts being left open. As a rule a double ligature was applied; in some cases the duct was divided to insure closing of the channel. The animals were kept alive for five or six months; they appeared perfectly well and thin ones gained in weight. No jaundice appeared. Five or more months after operation the cats were killed with chloroform.

Microscopically the left lobe showed a slight degree of granulation of the surface, the granules corresponding to the hepatic lobules. The right lobe remained normal. The bile passages were dilated but otherwise differed little from those on the right.

Comparison of microscopical sections from the right and the left lobes showed little difference in the general appearance of the hepatic cells on the two sides, though on the left side the individual hepatic cells were irregularly granular, and the cell columns were generally narrower and clearer than on the right. "On the left side, however, there was found a development of intralobular tissue separating the hepatic lobules, while on the right side there was no such interstitial tissue, or at the most, in some sections a few nuclei were noted lying between a limited number of lobules. The increase of connective tissue on the left side was most marked in those animals which had been kept alive the longest, and in these cases there was a slight shrinking of hepatic lobules which appeared to contain here and there new cells."

There appears to be a considerable range of normal variation in the gross anatomy of the biliary tract and in the width of the various lumina. When the lumen is unusually narrow, or where traction, pressure or other force tends to obliterate it, it seems probable that the walls of the duct might adhere and patency be lost. This is rendered more likely by the fact that little biliary secretion passes through the ducts in the early months of development. Indeed, almost nothing passes; while biliary acids and bile pigments have been demonstrated in the meconium as early as the third month of intra-uterine development, it is not until shortly before birth that any appreciable amount of bile pigment is excreted by this path (Ylppö).¹⁴ Such an obstruction might be caused, accompanied or followed by a catarrhal process, and this might increase the extent of the lesion.

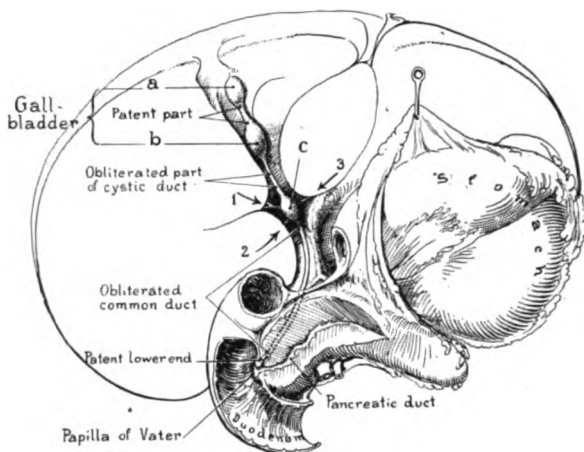


Fig. 6.—Diagram explanatory of drawing of specimen shown in Figure 5.

After birth, and after the invasion of the gastro-intestinal tract by micro-organisms, catarrhal processes in the biliary passages are not uncommon. It seems probable that these may, in rare instances, lead to obliterations of the duct that closely simulate the congenital condition. Among the recorded cases of congenital atresia of the bile ducts there are several in which the symptoms developed at a considerable period after birth; Lotze, three months, slight jaundice before; Köstlin, six months; Treves, three years; Parker, four years, etc. In some of these cases, for example, a congenital narrowing of the ducts may have been present in the first place, followed later by actual obstruction and loss of patency and the development of characteristic symptoms.

14. Ylppö, Arvo: Icterus neonatorum (incl. I. n. gravis) und Gallenfarbstoffsekretion beim Foetus und Neugeborenen, Ztschr. f. Kinderh., Orig., 1913, ix, 208.

SYMPTOMS

The most striking symptom in congenital atresia or obliteration of the common bile duct is the jaundice. This usually appears soon after birth and steadily increases until it becomes intense and the skin assumes a greenish-yellow hue. The jaundice may not appear for several days. It is said that none of the cases seen by physicians immediately after birth showed jaundice at that time (Glaister, Witzel); the icterus became visible in from two to five days. Ylppö seems to have explained this fact by showing, first, that the liver normally produces little bile pigment till the time of birth; and, second, that the liver has capacity for storing a certain amount of bile pigment, and that not until this is overcome does the concentration in the blood rise to the level necessary for the production of cutaneous jaundice.

In Giese's case and in Hawkin's jaundice was first observed after eight days; in Morgan's and Thomson's, after ten days; in Wilk's and Westermann's, after fourteen days; while in Parker's case it appeared only after three weeks, and in Skormin's case, after five weeks. Yet in the second, third, sixth, seventh and eighth of these cases the ductus choledochus was found at necropsy to be represented by a mere connective tissue string, and in Thomson's and Giese's cases the ducts were wanting at the hilus.

In Köstlin's case the jaundice did not appear until the age of 6 months, and in Treve's case and W. S. Parker's case the jaundice appeared at 3 years.¹⁵ Other factors would seem to be operative in such cases.

In Weiss' case, cyst of the ductus choledochus in a 6-year-old boy, it was thought that the duct must have been more or less patent at various times during life, though the obstruction was complete at the time of section, since the stools were not acholic until a short time before operation and death. In this case the cyst formation was ascribed to unknown mechanical conditions that had obstructed the flow of bile more or less completely from time to time. Dusman,¹⁶ in discussing some cases of "idiopathic choledochus cyst," assumed that congenital weakness of the wall was coupled with some degree of swelling of the mucosa at the duodenal end and that distention of the duct resulted, followed by incomplete recovery and recurrence of the process. He cited cases in girls of 18 to 28 years. It is said also that there are

15. Benecke saw a case in a girl of 19 years in whom jaundice, without acholia, has been present from birth with an exacerbation, following trauma (?) at 10 years. The patient was operated on by Ausschütz; only stenosis of the ducts was found. This was thought to be congenital and the case to be a milder degree of the condition found in Treves' case. The occurrence of such cases as this and the above-mentioned ones increase the difficulties of classification.

16. Dusman, quoted by Weiss (Footnote 3).

cases of atresia of the common duct in which considerable bile passes into the intestine through other and accessory passages.

The stools are, as a rule, very pale or white.¹⁷ Even the meconium stools may be white. As Thomson pointed out, a deceptive coloring of the stool may be occasioned by bacterial action during a passing digestive disturbance (see condition of my case on March 1 as described in the case history). The urine may show little change or may be variously tinted, even to a dark bronze.¹⁸

The liver may be enlarged at birth or soon after, and as a rule becomes much enlarged; the spleen also may become enlarged.

Hemorrhages beneath the skin and mucous membranes are common, though they do not usually occur until after some weeks have passed. There may be bleeding from the nose, stomach and intestines and also from the umbilicus. Slight puncture wounds may prove to be the seat of uncontrollable oozing. Subcutaneous nodules may be formed. The pulse is usually not influenced by the icterus.¹⁹

When the obstruction to the flow of bile is complete, death usually occurs after a few weeks. In the fifty cases analyzed by Thomson, nine of the patients lived less than a month, and fewer than one third lived over four months. Lotze's patient, with an impervious hepatic duct, lived eight months, Niemann's nine months, Koplik's ten months.

While these patients are usually well nourished during the first weeks, emaciation later sets in. This, Thomson thinks, is "mainly due to secondary organic changes in the liver tissue interfering increasingly with the other more important functions of the organ and with the part it should play in the general metabolism of the body." In late cases the degree of cirrhosis present may be extreme.

Convulsions may be the terminal event. These may be due to cerebral hemorrhage, as in Ylppö's recent case, in which cortical bleeding in the hemispheres was found at necropsy, or they may be agonal.

17. There is some difference of opinion as to whether a certain amount of the bile gains entrance to the lumen of the intestines by way of the heavily jaundiced mucosa. Chase (*Newer Methods of Diagnosis of Pathological Conditions of the Liver*, Jour. Am. Med. Assn., 1912, lix, 329) has recently shown how unreliable are some of the tests that have been employed for bile in the stools.

18. Others have claimed that the urine is not colored by bile pigments in icterus neonatorum, or for a time, at least, in congenital obliteration of the bile ducts, as the infant's body does not at first possess the ability to put bile pigments into solution. Knöpfelmacher (in Pfaundler and Schlossmann's *Handbuch*) stated that this power is brought about by disease. The usual tests are sometimes positive. The tests more commonly used for bile and bile pigments in the urine have also been criticized.

19. The icterus of the newly born and that of older children also is usually unaccompanied by any slowing of the pulse rate. This must apparently be attributed to the fact that the bile of children contains only small quantities of the biliary acids. Jakuowitsch's analyses of the bile of children showed glycocholic, but no taurocholic, acid (Knöpfelmacher in Pfaundler and Schlossmann's *Handbuch*).

Suggestive family histories are to be found in some cases of congenital malformation of the bile ducts, and some have thought that there may exist a predisposition toward the production of these anomalies. Thomson reviewed the facts in certain of these cases, and Benecke inclined toward such a view, but later writers have rejected it.

Studies on the nitrogen and fat absorption of these infants have been made by Niemann²⁰ and Koplik,²¹ and these studies show that the nitrogen metabolism is normal, being from 80 to 93 per cent., but that the fat metabolism is greatly disturbed, the absorption being from 28 to 48.4 per cent., the usual percentage being from 88 to 96, and that if the pancreatic ducts are patent the pancreatic secretion is of normal strength, but that the lipolytic ferment acts weakly on account of the absence of the bile salts, which normally increase the strength of the ferment ten to twenty times.²²

DIAGNOSIS

Icterus is a common phenomenon during the first few weeks of life. It occurs as icterus neonatorum in 30 to 80 per cent. of all newly born infants. It usually appears about the third day, increases in severity for two or more days, and then slowly disappears. In moderately severe cases it may be marked for about a week, in severe cases for about two weeks.

When icterus persists for longer than two weeks, and when it increases in intensity toward the end of the second or third week, a more serious condition should be suspected. This may prove to be sepsis. In the current texts sepsis in the infant is commonly said to be accompanied by jaundice. Ylppö's observation that icterus neonatorum pursues its usual course uninfluenced by concurrent sepsis, brings this teaching into question. In any event other symptoms are commonly

20. Niemann: *Ztschr. f. Kinderh.*, 1912, iv, 152.

21. Koplik and Crohn: *Fat and Nitrogen Metabolism in a Case of Congenital Absence of the Bile Ducts, etc.*, *AM. JOUR. DIS. CHILD.*, 1913, v, 36.

22. Similar studies have recently been made by W. S. Parker (*Metabolism of a Child with Complete Absence of Bile from the Intestines*, *AM. JOUR. DIS. OR CHILD.*, 1913, v, 386) upon a 4 year old boy in whom the bile ducts seem to have been patent until after the third year. At that time the stools became light colored, and bile and bilinogen were found to be absent from the stools. (A negative bilinogen test is considered by Chase as evidence of complete absence of the bile from the intestine). A large tumor the size of a grape-fruit was found in the gallbladder region. At operation the gallbladder was found to be normal, and also the right kidney. The tumor was a large cyst adherent to the liver below, to the colon on the inner side and to the deep structures posteriorly, while superiorly a prolongation of the cyst extended up behind the liver. Histologically the wall of the cyst resembled that of a gallbladder with chronic inflammation. A pint of greenish viscid bile was evacuated, and a fistula established. The lad continued to do well. Studies upon his metabolism resemble those made by Nieman and Koplik upon their infants of 9 and 11 months respectively.

present in sepsis, such as fever with usually an abnormal condition of the umbilicus. Micro-organisms may be found in the blood.

The condition may be syphilitic. Still²³ has emphasized the frequency with which jaundice appears in congenital syphilis. Others have not observed it so frequently. When seen it is usually present at birth, persists and may become intense. It may not appear, however, for some days or even weeks after birth. There may be hemorrhages into the skin or from the mucous membranes. The usual signs of syphilis are commonly present, and the Wassermann reaction is positive.

If sepsis and syphilis can be excluded, and if the icterus becomes more intense toward the end of the first month, the probability of obstructive jaundice must be considered.²⁴

CONDITIONS THAT MAY BE PRESENT

Cholelithiasis is not unknown in infancy. Calculi may be present at birth. Still has collected from the literature fourteen cases in infants under 10 months of age. There are a number of instances (Maxwell,²⁵ Murchison, etc.) in which the obstruction has proved to be a plug of inspissated bile. Some have thought that in early infancy there is a tendency for the bile to become viscid and to stagnate.

Persistent congenital icterus may be present, as described by Parke Weber,²⁶ and held by him to be due to a partial obliteration of the bile ducts, that entirely disappears. Such cases may be instances of icterus neonatorum gravis (seu prolongatus), in which icterus neonatorum simplex persists for several weeks or even for many years (Ylppö) and then gradually disappears, or they may be cases of congenital obliteration or atresia of the bile ducts. The lesion, or atresia, may be complete or partial; accessory passages may be present or there may be merely stenosis with secondary blocking of the passage.

When the obstruction is complete, bile pigments will be absent from the intestines. When the obliteration includes the papilla of Vater and there is no compensation through the duct of Santorini or through

23. Still, G. F.: *Common Disorders and Diseases of Childhood*, Oxford Press, 1912.

24. Simple catarrhal jaundice is a condition that comes into consideration in older infants and young children. It is infrequently met with in children under two years of age, and is extremely rare during the first year of life. Individual cases, however, have been observed as early as the fourth and eighth week, and perhaps a dozen cases have been reported in infants under a year (see Hempelmann, T. C.: *AM. JOUR. DIS. CHILD.*, 1915, x, 39). It is difficult to understand, as Hempelmann says, why simple catarrhal jaundice should be so rare at this age, when gastro-enteritic disorders due to dietetic errors or to bacterial invasion, two factors supposed to favor the occurrence of jaundice, are so common.

25. Maxwell, Adams: Cited by Blake White, *Am. Jour. Obst.*, 1888, xxi, 48.

26. Weber, F. Parke: *Edinburgh Med. Jour.*, 1903, lvi, 3.

an abnormally placed duct of Wirsung, pancreatic secretions will also be absent from the lumen of the intestine. This may be readily demonstrated by the use of the duodenal catheter and appropriate tests, as recently shown by Hess.²⁷ Cases in which the pancreatic duct is also involved appear to be exceedingly rare.

The difficulties in establishing a satisfactory diagnosis of congenital obliteration of the bile ducts during the early weeks are many. An example is found in a case reported by Griffith in 1904. In this case the jaundice appeared shortly after birth and became intense. The stools were dark colored and the urine bile stained. An eruption of purpuric spots and subcutaneous hemorrhages appeared on the tenth day. At the third week traces of blood were seen at the umbilicus, and puncture of the toe at one week was followed by persistent, almost uncontrollable, oozing. Purpuric spots continued to appear. At the sixth week the jaundice began to clear up, a few cutaneous hemorrhages appeared, the stools soon became of a normal yellow, and the infant recovered.

The case reported by Carbonelle²⁹ seems to have resembled this; cerebral symptoms predominated.³⁰

PROGNOSIS AND TREATMENT

During the early weeks of life the prognosis in these cases must always be guarded, because of the uncertainty of having arrived at a correct diagnosis. In those cases in which pancreatic ferments are found, by repeated use of duodenal catheter, to be absent from the duodenum, it may be concluded that atresia involves the pancreatic ducts and that the outlook is hopeless. In many cases it would seem that with time alone can come increased certainty of diagnosis. When a definite tumor can be detected in the biliary region, an exploratory operation is clearly indicated. In other cases the prognosis is almost invariably hopeless, unless it shall prove possible to treat them surgically.

In those cases in which the common duct alone is involved it is possible that a skilful surgeon might utilize the gallbladder or other structures in such manner as to form an outlet for the bile. A review of the diagrams here presented shows that if the data given by the various authors have been correctly interpreted such a procedure was theoretically possible in 16 per cent. of all cases yet reported, perhaps in even more.

27. Hess, A. F.: A Consideration of the Pancreas and Its Ducts in Congenital Obliteration of the Bile Ducts, *Arch. Int. Med.*, 1912, x, 35.

28. Griffith, J. P. Crozer: *Arch. Pediat.*, 1905, xxii, 257.

29. Carbonelle: *An. de la Accad. de obst. (etc)*, Madrid, 1911, iv., 234.

30. An interesting case is that reported by Ford (cited in Footnote 12). The patient was an infant with tuberculosis of the cervical lymph glands. At the age of one and a half years deep jaundice appeared, with clay-colored stools and pigmented urine, and later the liver became enlarged. At necropsy there was found an inflamed gland at the hilus of the liver pressing upon and completely obstructing the common duct.

The cases in which it would seem that operation might have been performed with some hope of success are those of Blake White (12 days), Donop (2 months), L'Hommeau (3 months), Hawkins (4½ months), Morgan (9½ weeks), Glaister (3 days), Murchison (4 months), Danforth (3 days), Harley (4 days), Anderson (12 days), Wickham Legg (5½ months), Oxley (6 weeks), Treves (19 years), G. Parker (6 months), Fischer (14 weeks), Kynoch (3 months, 4 days), Berard (?), Elperin (16 days), Zuber (4 days), Weiss (6 years), Letulle (25 years), W. S. Parker (4 years), and probably also that of Formiggini (newly born).

It is uncertain whether to these may be added the cases of Westermann II, Hennig, Griffith I, Emmanuel, and possibly Virchow and Stieglitz, together with that of Rotgens (5 years).

The cases of Giese (unsuitable, Fig. 1), of Treves (successful), of W. S. Parker (successful), of Oxley (moribund), of Morse and Murphy (unsuitable, Fig. 3), and of Putnam (unsuitable, Fig. 1) were operated on.

In Oxley's case a tumor had been present since birth. When the child had become much emaciated and the abdomen much distended, a grooved needle, and afterward a Southey cannula, were inserted, and 36 ounces of bile drawn away in about twenty minutes. In W. S. Parker's case a pint of viscid bile was evacuated and a fistula established. In Treve's case cholecystenterostomy with a Murphy button was done. The button was passed in about a fortnight, and the second stool after operation contained bile, the first in sixteen years.

Rotgen's case was that of a 5 year old girl, who was without symptoms during the first year, and then became subject to attacks of colicky pain, with clay-colored stools and pigmented urine. These attacks became more numerous with increasing age. There was pain over the gallbladder region during attacks, and jaundice was observed in one attack. The child was small but well formed and well nourished; she was not anemic. A tentative diagnosis of cholelithiasis was made and the abdomen explored.

No stone was found but there was evidently some obstruction to the flow of bile at the papilla of Vater. The gallbladder and the cystic and common ducts were enlarged. It was thought that there must have been a congenital narrowing or valve-like obstruction in the common duct which persisted without symptoms up to the end of the first year and that subsequent dilatation of the common duct above the point must have caused kinking (compare Weiss' case, previously mentioned) and the symptoms noted.

An external fistula was established and all bile passed through this. The child became weaker and more emaciated. The opening was then obstructed by packing and gradually closed, but the attacks returned. Four months later the operation was completed by laying the dilated common duct and the duodenum side by side and making an opening for the passage of bile. The operation was successful, the wound healed perfectly, and the child became strong and well. During the next year she had a few attacks of short duration, supposedly due to catarrhal swelling of the new opening.

It is seen that of the cases anatomically suitable for operation, six died before the twentieth day of life, nine lived from two to six months, while four, or if Rotgan's case be included, 5, were over 4 years of age.

TYPE OF OPERATION

It would seem that exploratory laparotomy is justified as soon as the diagnosis can be established with reasonable certainty. If the child is evidently maintaining his general nutrition, exploration might be deferred. It should not be deferred until bleeding or evident loss of weight appears.

If on exploration the diagnosis of congenital obliteration (atresia) of the bile ducts is confirmed, and if the anatomical conditions present permit, anastomosis between some portion of the biliary tract, usually the gallbladder, and the duodenum should be attempted.

If such an anastomosis cannot be made at the time of exploration, an external fistula for the escape of the bile should be established when possible. A repair operation might later be attempted. This procedure is less desirable because of the greater danger of infection at the time of the second operation.³¹

That the patient's nutrition can be maintained in the meantime would seem to be indicated by the conditions found in W. S. Parker's case.²² The patient's own bile, or bile salts derived from it or from other sources, might be administered by mouth or through a duodenal catheter.

CONCLUSIONS

Congenital obliteration (atresia) of the larger bile ducts is not an extremely rare condition. It deserves more attention from clinicians.

Accumulating evidence tends to show that the condition is usually a developmental anomaly and not the result primarily of inflammatory processes.

In at least 16 per cent. of all cases yet reported the anatomical relations are such that operative relief is theoretically possible.

Recent surgical experiences in young children afford clinical basis for such hopes.

In view of the otherwise hopeless nature of the case, the biliary tract should be explored as soon as the diagnosis is sufficiently estab-

31. J. H. Jacobson (Repair and Reconstruction of the Bile Ducts, *Am. Jour. Obst.*, 1914, lxx, 948) has recently considered at some length the repair and reconstruction of bile ducts; as have also J. F. W. Ross (*Canad. Pract.*, Toronto, 1893, xviii, 401) and C. B. Davis and D. I. Lewis (Repair of the Common Duct by Means of Transplanted Fascia, *Tr. West. Surg. Assn.*, 1913, Minneapolis, 1914, p. 217). The first named reviews the literature of the subject.

lished, and if the anatomical relations permit—16 per cent. of published cases—an artificial passage for the bile to the duodenum should be made.

When for any reason this cannot be done at the time of exploration, an external outlet for the bile should be provided. A repair operation may be attempted at a later date.

Meanwhile the child's nutrition should be maintained by the administration, if necessary, of bile or bile salts.

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THE NONPROTEIN NITROGENOUS CONSTITUENTS OF THE BLOOD AND THE PHENOLSULPHONE- PHTHALEIN TEST IN CHILDREN *

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During the past few years the determination of the nitrogenous constituents of the blood has been rendered much more simple and accurate by the improved methods of Folin and Denis,¹ Marshall and Davis,² Van Slyke and Cullen,³ Benedict,⁴ and others. Previous to the studies of Folin and his co-workers very little, if any, dependence could be placed on the quantitative analysis of the blood for its nonprotein nitrogenous constituents.

BLOOD IN ADULTS

The results of many investigations of the chemistry of the blood have recently appeared in the literature, and, as a result, standard figures for adults are now available.⁵

The total nonprotein nitrogen of the blood has been demonstrated to be the index of the efficiency of the kidney in removing waste nitrogenous products circulating in the blood. It has been conclusively shown that the total nonprotein nitrogen is increased in the blood in certain forms of kidney disease, and that a definite diagnosis of impaired renal function can be made by this examination of the blood. Normally the total nonprotein nitrogen varies between 25 and 40 mg. per 100 c.c. of blood. In cases of severe chronic nephritis with uremic

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4. Benedict: Jour. Biol. Chem., 1915, xx, 629.

5. Farr and Austin: Jour. Exper. Med., 1913, xviii, 228. Farr and Krumbhaar: Jour. Am. Med. Assn., 1914, lxiii, 2214. Foster and Davis: Am. Jour. Med. Sc., 1916, cli, 49. Foster: Arch. Int. Med., 1914, xiii, 452; 1915, xv, 356. Frothingham, Fitz, Folin and Denis: Arch. Int. Med., 1913, xii, 245. Frothingham and Smillie: Arch. Int. Med., 1914, xiv, 541. McLean and Selling: Jour. Biol. Chem., 1914, xix, 31. Meyers and Fine: Proc. Soc. Exper. Biol. and Med., 1913, xi, 132; Jour. Biol. Chem., 1915, xx, 391.

manifestations the nonprotein nitrogen, according to several investigators, may amount to 300 mg., or even more. Furthermore, it has been shown that cases of nephritis having figures above 60 mg. usually end fatally.

The *urea nitrogen* of the blood amounts to about 50 per cent. of the total nonprotein nitrogen. Most investigators give as normal figures 12 to 20 mg. per 100 c.c. of blood. The variations in the urea nitrogen closely parallel the total nonprotein nitrogen.

The normal *uric acid* content of the blood is from 1 to 2 mg. per 100 c.c. It is usually increased in cases of severe nephritis, gout and lead poisoning.

Creatinin was first suggested by Neubauer⁶ as an index of renal function. According to Folin and Denis,⁷ the kidneys remove creatinin from the blood with remarkable ease, and except in cases of extreme retention, the creatinin of the blood remains at the normal level. Normally the blood contains from 1 to 2 mg. of creatinin per 100 c.c. Myers and Lough⁷ have demonstrated that a creatinin concentration over 2.5 mg. is almost invariably found only when renal involvement exists. Creatinin values from 3 to 5 mg. are regarded as decidedly unfavorable from a prognostic point of view, while figures over 5 mg. probably indicate an early fatal termination.

BLOOD IN CHILDREN

Since these newer methods of blood examination have been introduced, very few studies have been made in children. Schlutz and Pettibone⁸ recently reported the results of their examination of the blood for total nonprotein nitrogen and urea in some newly born infants. Tileston and Comfort⁹ have examined the blood of children for total nonprotein nitrogen and urea. The results of these investigators correspond very closely, as far as they go, with figures obtained in adults.

No reports have as yet been made on examinations for uric acid and creatinin in the blood of children. Before any accurate studies, analogous to those made in adults, are possible, the normal figures in children must be definitely established. We therefore determined to examine the blood for total nonprotein nitrogen, urea, uric acid, and creatinin in a series of children free from renal disease to determine if the results obtained corresponded with those found in normal adults. During the investigation a number of cases with renal involvement

6. Neubauer: München. med. Wchnschr., 1914, lxi, 857.

7. Meyers and Lough: Arch. Int. Med., 1915, xvi, 536.

8. Schlutz and Pettibone: AM. JOUR. DIS. CHILD., 1915, x, 206.

9. Tileston and Comfort: AM. JOUR. DIS. CHILD., 1915, x, 278.

were examined. These are included in our report; we reserve for a future communication, however, a detailed study devoted to nephritic cases alone.

TECHNIC

The phenolsulphonphthalein test was performed in each case by intramuscular injection, according to the method of Rowntree and Geraghty,¹⁰ and the total amount of the dye-stuff excreted in two hours was determined.

Method of Procuring Blood.—Thirty c.c. were withdrawn under aseptic precautions from a vein at the bend of the elbow into a small glass bottle containing a few crystals of potassium oxalate to prevent clotting. There has been no difficulty in obtaining this amount of blood. Untoward effects were never observed, even in very young children. The blood was taken in the morning before breakfast, about fourteen hours after the last meal.

We have employed, with slight modifications, Folin and Denis's¹ method for nonprotein nitrogen, Van Slyke and Cullen's² procedure for urea, Benedict's³ modification of Folin and Denis' method for uric acid, and Myers and Fine's^{4, 11} modification of Folin's method for creatinin. In our studies the Hellige colorimeter was used.

Nonprotein Nitrogen.—Into a 50 c.c. volumetric flask, which has been half filled with methyl alcohol, free from acetone, 5 c.c. of blood is pipetted. This is made up to volume with alcohol, shaken thoroughly, and allowed to stand for two hours. After being filtered into a wide-mouth test tube, from 3 to 4 drops of a saturated alcoholic solution of zinc chlorid are added, and the whole is refiltered. This second filtrate should be clear. Ten c.c., equivalent to 1 c.c. of blood, is placed in a Jena glass test tube (120 by 20 mm.), and about 0.4 gm. potassium sulphate, 1 drop of 10 per cent. copper sulphate, 1 c.c. of concentrated sulphuric acid, and from 4 to 6 drops of kerosene are added. The test tube is then placed into a beaker of warm water and slowly heated until all the alcohol has been driven off. The tube is removed from the beaker, dried, and heated over a microburner until the fluid is perfectly clear, and, as a rule, colorless. It is then allowed to cool. Five c.c. of distilled water are then added. The tube is placed into one of the cylinders of the aerating apparatus, and connected at once with another aerating cylinder containing 20 c.c. distilled water and 1 drop of concentrated hydrochloric acid. The cylinder containing the tube is opened, 5 c.c. of concentrated sodium hydroxid are added, and it is then immediately closed. The ammonia is aerated for one-half hour. Diluted Nessler's solution is added to the cylinder into which the ammonia has been aerated, the unknown solution is made up to volume and compared in the colorimeter with a standard solution containing 1 mg. of nitrogen. From the reading obtained the amount of nitrogen in the unknown is calculated from the tables furnished by Myers and Fine.¹¹

Urea.—Into a wide-mouth test tube 2 c.c. of blood are pipetted, and $\frac{1}{10}$ gm. soy bean urease (Arlco-Urease), is added, and about 2 c.c. distilled water. This is incubated for five minutes at 50 C. (122 F.). The tube is then removed from the incubator. The foaming inhibitor and an equal volume of saturated potassium carbonate are added. The tube is then placed in a cylinder of the aerating apparatus and the ammonia aerated. The nitrogen is calculated as in the nonprotein nitrogen estimation above.¹¹

Uric Acid.—Twenty c.c. of blood are pipetted into a 375 c.c. casserole, and five volumes of freshly prepared hundredth-normal acetic acid. The casserole is placed on a water bath, the contents stirred, and heated until coagulation occurs. The casserole is then heated over the open flame and 2 teaspoonfuls of thick alumina cream are added. The sides of the casserole are washed

10. Rowntree and Geraghty: Jour. Pharmacol. and Exper. Ther., 1910, i, 579; Arch. Int. Med., 1912, ix, 284; 1913, xi, 121.

11. Myers and Fine: Essentials of Path. Chem., 1913.

with hot water and the solution again heated for a few minutes. The solution is then poured through hardened filter paper into a 250 c.c. graduated cylinder. The filtrate should be absolutely clear. The coagulum is washed back into the original casserole with hot water, heated, and refiltered, the same filter paper being used. To the combined filtrates 1 drop of glacial acetic acid is added. The solution is evaporated on the water bath down to about 3 c.c., and transferred to a 15 c.c. conical centrifuge tube. The casserole is flushed out with a little hot water, and the washings added to the tube. The total volume should amount to about 10 c.c. The tube and contents are centrifuged, the supernatant liquid poured off into another centrifuge tube and, when cool, 15 drops of silver magnesia are added. The solution is then thoroughly mixed and placed in the ice box for fifteen minutes. The tube is again centrifuged and the supernatant liquid decanted. The lip of the tube is dried with filter paper. The ammonia is volatilized by suction. To the sediment in the tube is added 1 or 2 drops of 5 per cent. potassium cyanid and 2 c.c. of Folin-Macullum reagent. The solution is transferred to a 50 or 100 c.c. graduated cylinder, and 20 c.c. of saturated sodium carbonate added. The mixture is then diluted to 50 or 100 c.c. with water, depending on the intensity of the color, and compared in the colorimeter with a standard solution containing 1 mg. of uric acid. The amount of uric acid present is calculated from the tables.¹¹

Creatinin.—Two c.c. of blood are pipetted into a glass centrifuge tube (130 by 12 mm.), and 8 c.c. of distilled water are added. After the corpuscles have been laked, about 1 gm. of dry picric acid is added, and the mixture stirred with a glass rod until the whole mass assumes a light yellow color. It is then centrifuged and the supernatant liquid filtered. Two c.c. of the filtrate is placed in the cup of the colorimeter and 0.1 c.c. of 10 per cent. sodium hydroxid is added. The mixture is allowed to stand for ten minutes. It is then compared with a standard solution of creatinin to which the same percentage of sodium hydroxid has been added, and which has been allowed to stand for ten minutes. The amount of creatinin is calculated from the tables of Myers and Fine.¹²

The results of the blood examination in fifty hospital children without any evidence of renal disease are shown in Table 1. In Table 2 are recorded the blood analyses of sixteen children in whom there was demonstrated, at the period of examination, some evidence of renal involvement. The figures represent in milligrams the respective amounts of nonprotein nitrogen, urea, uric acid, and creatinin per 100 c.c. of blood. The phthalein excretion for two hours is given in each case.

DISCUSSION OF TABLE 1: CHILDREN FREE FROM RENAL DISEASE

Nonprotein Nitrogen.—The nonprotein nitrogen varied between 19 and 40 mg. per 100 c.c. of blood. The average amount in fifty children was 28 mg. These figures correspond very closely with the values between 15 and 43 mg., as given by Farr and Austin⁸ and some other investigators of adult blood. They are somewhat higher than those found by Folin and Denis (22 to 26 mg.). It should be stated, however, that the latter call attention to the fact that, when other than perfectly healthy persons are examined, higher values than from 22 to 26 mg. are obtained even though there are no evidences of renal disease. Attention was called to the fact that our observations were made on children who were hospital patients, and this may account for our slightly higher figures. Furthermore, according to Agnew¹² a nonprotein nitrogen

12. Agnew: Arch. Int. Med., 1914, xiii, 485.

TABLE 1.—ANALYSES OF THE BLOOD OF CHILDREN FREE FROM RENAL DISEASE

Case	Age, Years	Sex*	Weight, Pounds	Blood Analysis				Phenol-sulphone-thaleïn, Per Cent.	Diagnosis
				Non-protein N, Mg. per 100 c.c.	Urea N, Mg. per 100 c.c.	Uric Acid Mg. per 100 c.c.	Creatinin, Mg. per 100 c.c.		
5271	12	♀	68½	37	10	2.6	1.1	74	Postscarlatinal paralysis
7563	13	♂	72½	37	12.5	2.7	1.1	66	Malaria
7834	9	♂	..	26	11.5	1.8	1.1	85	Osteomyelitis of patella
7203	7	♀	49	26	13	1.9	1.0	66	Thyroglossal cyst
7967	10	♂	..	31	13	0.8	0.5	92	Luetic synovitis
7902	10	♂	..	27	11	3.1	0.8	66	Undescended testicle
7809	8	♀	..	22	10	1.1	1.0	81	Appendicitis
7989	8	♂	55	20	10.5	1.3	0.6	79	Tuberculosis
7036	2	♀	25	30.5	10.5	1.4	0.6	58	Adenites
7986	6	♂	44	31.5	10.5	2.1	1.3	77	Cardiac
8148	12	♀	59	33	16	2.3	0.9	75	Frost bite
8169	12	♀	..	26	11	2.7	0.7	71	Appendicitis
8170	9	♀	44½	35	21	1.3	0.8	88	Cardiac
8127	8	♂	51	38	13	1.8	0.8	76	Pneumonia, after crisis
8201	10	♂	68	40	15	1.8	1.1	81	Neurosis
8244	8	♀	52	29.5	12.5	1.5	1.1	79	Appendicitis
8251	5	♂	37	22	11	1.3	1.2	77	Grippe
8367	6	♂	36	33	12.5	1.9	0.5	85	Jaundice
7912	6	♀	39	30	10.5	1.9	0.5	87	Grippe
2141	6	♀	40	23	8.5	1.5	1.5	80	Little's disease
7022	12	♂	69	31.5	10.5	2.1	2.4	81	Typhoid convalescence
6691	9	♂	65	31	12.5	2.1	1.5	71	Typhoid convalescence
8533	7	♀	42	28	11	2.5	2.4	96	Pulmonary tuberculosis
8446	5	♂	38	32	13	3.2	2.8	65	Muscular rheumatism
7111	12	♀	64	19	10	0.8	0.9	87	Cardiac
7848	7	♀	46	20	9.5	1.8	1.1	71	Burn
172	6	♀	44	30.5	12.5	1.9	2.2	65	Unresolved pneumonia
197	8	♂	61	27	13	1.3	2.4	75	Chorea
194	13	♀	89	27	13	2.3	1.7	58	Rheumatism
157	9	♀	48	20	8	2.4	0.9	73	Cardiac
213	13	♀	54	26	10	1.5	2.5	74	Incipient tuberculosis
124	6	♀	39	26	10	1.1	2.2	87	Cardiac
279	5	♂	47	30	9	2.3	4.0	74	Marked constipation; Hirschsprung's dis.
322	14	♀	57	26	9	2.8	2.4	84	Appendicitis
385	8	♀	55	31	15	1.8	2.4	76	Neurosis

* ♂ denotes male; ♀, female.

TABLE 1.—ANALYSES OF THE BLOOD OF CHILDREN FREE FROM RENAL DISEASE—(Continued)

Case	Age, Years	Sex*	Weight, Pounds	Blood Analysis				Phenol-sulphone-thalein, Per Cent.	Diagnosis
				Non-protein N, Mg. per 100 c.c.	Urea N, Mg. per 100 c.c.	Uric Acid, Mg. per 100 c.c.	Creatinin, Mg. per 100 c.c.		
150	5	♂	39	31	11.5	1.1	2.1	66	Asthma
347	9	♂	58	36	9.5	1.8	2.1	70	Endocarditis
396	5	♂	34	28	12.5	0.7	2.2	60	Incipient tuberculosis
7579	7	♂	47	27	18	3.1	1.1	55	Appendicitis
427	5	♂	47	33	14	2.0	2.4	65	Epilepsy
319	4	♀	34	25	11.5	1.3	1.7	64	Pertussis
407	8	♀	38	23	8	1.6	1.6	60	Lobar pneumonia
625	9	♀	54	26	11.5	2.0	1.8	62	Asthma
361	6	♂	39	29	11.5	1.5	2.5	64	Cervical adenitis
740	8	♂	51	31	9.5	2.1	1.6	65	Gastro-enteritis
889	4	♂	31	26	11	2.8	1.0	50	Epilepsy
708	4	♂	35	31	12.5	1.1	0.6	50	Purpura haem.
1058	13	♀	63	38	12.5	1.6	1.5	60	Pulmonary tuberculosis
1147	9	♂	59	32	15.5	2.0	1.9	65	Cardiac
1411	7	♂	54	30	9.0	1.6	1.1	70	Pulmonary tuberculosis

* ♂ denotes male; ♀, female.

content of 40 or even higher does not, in this class of cases, necessarily imply a clinical renal insufficiency. On the other hand, according to Farr and Krumbhaar¹ the moderate increase rarely seen in presumably normal adults may be due to slight renal involvement not demonstrable by chemical tests.

Urea.—The urea in our series varied between 8 and 21 mg. per one hundred c.c. of blood. The average in fifty cases was 12 mg. These figures correspond very closely to those given for adults. This also holds true for the relation of urea to total nonprotein nitrogen, which was about 50 per cent.

Uric Acid.—The uric acid in our cases varied between 0.6 and 3.2 mg. The average uric acid in fifty cases was 1.8 mg. These figures closely parallel those for adults. The highest figure obtained among our cases without renal involvement was 3.2 mg., and occurred in a child suffering from muscular rheumatism.

Creatinin.—The creatinin in our series varied between 0.5 and 4 mg. The average of all our cases was 1.5 mg. These figures correspond with those recorded in adults. Only one case showed a creatinin retention above 2.8 mg. This occurred in a boy 5 years of age, with an enormously enlarged colon, and suffering from marked constipation. The creatinin in this case was 4 mg.; the total nonprotein nitrogen, urea, uric acid, as well as the phenol-sulphonephthalein test were all within normal limits. Inasmuch as retention of creatinin occurs only in nephritis (Myers and Lough), we are unable to give an explanation for the rather high retention of creatinin observed in this case.

Phenolsulphonephthalein Test.—The total phenolsulphonephthalein excretion for two hours in our cases varied between 50 and 96 per cent., with an average

of 70 per cent. These figures are in accord with those given for adults (50 to 85 per cent.); they are, however, slightly lower than those of Tileston and Comfort,* who found that the average phenolsulphonephthalein excretion in children was from 78 to 81 per cent.

DISCUSSION OF TABLE 2: CHILDREN WITH RENAL DISEASE

The cases fall into four groups: (1) acute nephritis; (2) chronic nephritis; (3) passive congestion, and (4) renal neoplasms.

The number of cases (sixteen) is of course too small to permit absolute conclusions to be drawn. As stated above, the chief object of this paper is

TABLE 2.—ANALYSES OF THE BLOOD—

Case	Age, Years	Sex*	Weight, Pounds	Non-protein N. Mg. per 100 c.c.	Blood Analysis			Urine Analysis	
					Urea N. Mg. per 100 c.c.	Uric Acid, Mg. per 100 c.c.	Creatinin, Mg. per 100 c.c.	Phthalein, Per Cent.	Sp. Gr. Albumin
6769	7	♀	43	30	12.5	4.2	0.4	85	1.018 Large Amt.
7863	8	♀	44	31	11.5	1.7	1.0	69 Large Amt.
7728	4	♀	31	25	10.5	1.4	0.5	74	1.021 Moderate Amt.
920	8	♂	40	25	10	0.7	0.6	60	1.015 Faint trace
1394	2	♀	24	24	11.5	2.9	0.6	23	1.012 Large Amt.
7274	9	♀	78½	41	16	0.7	0.6	19	1.020 Large Amt.
8067	2	♂	23	52	23	3.6	1.2	44	1.019 Large Amt.
H.I.A.	6	♀	37	47	12	4.2	0.8	73	1.015 Trace
330	8	♀	42	34	12.5	3.5	3.3	64	1.027 Trace
H.I.A.	25 mos.	♀	28	41	20.5	4.0	1.1	33	1.000 Large Amt.
540	22 mos.	♀	26	37	12.5	3.1	1.7	30 Negative
685	9	♂	64	37	12	1.8	1.3	58	1.023 Faint trace
1047	7	♀	41	26	13	2.1	1.5	40	1.018 Faint trace
783	8	♀	43	27	13	2.7	1.5	42	1.018 Faint trace
1136	6	♂	47	26	12.5	0.8	1.7	38	1.020 Large Amt.
460	7	♂	47	35	12.5	1.7	2.4	78	1.019 Faint trace

* ♂ denotes male; ♀, female.

the presentation of normal figures. The detailed study of nephritic cases is now being continued, and will be presented in a future communication.

Acute Nephritis.—The total nonprotein constituents in all the five cases can be considered within normal limits. The phthalein excretion, on the other hand, was diminished. These findings correspond with those noted for adults. Frothingham and Smillie⁵ and others have shown that the phthalein excretion as a rule is diminished in cases of acute nephritis, whereas the total nonprotein constituents are, or may be, normal. As Myers and Lough¹ express it, "In the early stages of nephritis the phenolsulphonephthalein test probably yields the more valuable information, but after a decided retention has taken place, the nonprotein and urea nitrogen of the blood furnish a much more accurate index of the changes in the condition of the patient."

Chronic Nephritis.—The five cases of chronic nephritis show an increase in the nonprotein constituents of the blood. With the increased nitrogen retention there was a diminished phenolsulphonephthalein excretion. It has been shown¹ that in chronic nephritis an increase in uric acid is generally the first evidence of retention. This is clearly demonstrated in our cases. The urea nitrogen is increased next, while large amounts of creatinin in the blood are seen only in cases of severe nephritis. On the other hand, it must be borne in mind that normal nonprotein nitrogen constituents may be present in cases of severe chronic nephritis, even with uremia.²

—OF CHILDREN WITH RENAL DISEASE

Urine Analysis	Blood Pressure mm. of Hg	Diet	Diagnosis	Remarks
Microscopical				
Moderate granular casts....	S. 90 D. 70	Soft, salt free	Acute nephritis.....	Condition improved
Many hyaline and granular casts	Soft	Acute nephritis	
Moderate hyaline and granular casts	Soft	Acute nephritis	
Few hyaline and granular casts and R. B. C.	S. 100	Soft	Acute nephritis	
Many hyaline and granular casts and R. B. C.	S. 95	Soft	Acute nephritis	
Many hyaline, granular and waxy casts	S. 125 D. 95	Soft, salt free	Chronic nephritis.....	Severe edema Total N 2.23 gm. } 61% Urea N 1.4 gm. }
Many granular casts and R. B. C.	Soft, salt free	Chronic nephritis.....	Condition unimproved
Few hyaline and granular casts; R. B. C. and pus cells	Soft	Chronic nephritis.....	Total N=6.29 gm. } 75% Urea N=6.2 gm. }
Many pus cells.....	S. 72	Soft	Chronic nephritis.....	Condition unimproved
Many hyaline and finely granular casts, few R. B. C.	Soft	Chronic nephritis	
Negative	Soft	Sarcoma of kidney	
Few hyaline casts.....	S. 110 D. 60	Soft, salt free	Passive congestion	
Occasional granular casts, Few R. B. C.	S. 105	Soft, salt free	Passive congestion.....	Condition unchanged
Occasional granular and hyaline casts	S. 115	Soft	Passive congestion.....	Condition unchanged
Many hyaline casts.....	S. 110	Soft	Passive congestion.....	Condition improved
Few granular casts.....	Soft	Passive congestion.....	Condition improved

Passive Congestion.—Our five cases of passive congestion showed a practically normal nonprotein nitrogen blood condition. The phenolsulphonephthalein excretion, on the other hand, was decreased, and in some cases markedly so. It would appear that one can at times differentiate cases of chronic nephritis from passive congestion by a chemical examination of the blood alone. In children as in adults, apparently the phenolsulphonephthalein excretion is influenced by passive congestion, but the nonprotein constituents of the blood are not.

Neoplasms.—We have observed one case of sarcoma of the kidney in a child 22 months of age. The urine was normal. The total nonprotein nitrogen was within normal limits. The uric acid was slightly increased. The phenol-sulphonephthalein excretion was markedly diminished—30 per cent. in two hours.

SUMMARY

In a series of fifty children free from evidences of renal disease, chemical examination of the blood gave the following results: the total nonprotein nitrogen varied between 19 and 40 mg. per 100 c.c. of blood, the average being 28 mg.; the urea nitrogen varied between 8 and 21 mg., the average being 12 mg.; the uric acid varied between 0.6 and 3.2 mg., the average being 1.8 mg.; the creatinin varied between 0.5 and 4 mg., the average being 1.5 mg.; and the phenolsulphonephthalein varied between 50 and 96 per cent., the average being 70 per cent.

A smaller number (16) of cases with renal involvement were examined. Although this series is not large enough for final conclusions, the following hold true for the cases we have studied:

1. In acute nephritis the nonprotein nitrogen constituents were found within normal limits; the phenolsulphonephthalein excretion was diminished.
2. In chronic nephritis the nonprotein nitrogen constituents were usually increased, while the phenolsulphonephthalein excretion was diminished.
3. In passive congestion the nonprotein constituents were normal while the phenolsulphonephthalein was diminished.
4. In one case of sarcoma of the kidney with normal urinary findings the nonprotein constituents, with the exception of uric acid, were normal. The latter was slightly increased. The phenolsulphonephthalein excretion was diminished.

CONCLUSIONS

1. Figures for the nonprotein constituents of the blood as well as for the phenolsulphonephthalein excretion of children free from renal disease are practically identical with the figures obtained from adults, and vary within the normal limits as the adult figures vary.
2. The changes in these figures in children the subjects of renal disease corresponds, in our cases, with the changes observed in adults.
3. The importance of the tests for diagnosis and prognosis, amply demonstrated in adults, will, in all probability, hold true for children, although a more comprehensive series of cases are required definitely to establish this view.

We wish to express our gratitude to Drs. A. F. Orth and H. Cohn of the house staff of the German Hospital for their assistance.

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ADDITIONAL REFERENCES

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CUTANEOUS REACTION FROM PROTEINS IN ECZEMA *

KENNETH D. BLACKFAN

BALTIMORE

As the result of the studies of von Pirquet and Schick¹ serum sickness is regarded as being closely related to anaphylaxis. There are a number of other conditions also in which anaphylaxis has been considered to play an important etiologic rôle. Thus the so-called idiosyncrasies which occur in many people who suffer from urticaria, vomiting and angioneurotic edema after the ingestion of certain foods seem to depend upon an acquired or possibly an inherited hypersensitiveness to the particular protein involved.

It is not inconceivable that as our knowledge of this subject increases, a number of conditions may be shown to be dependent upon anaphylaxis. Meltzer² has called attention to the similarity between asthma and anaphylaxis, and in 1906 Wolff-Eisner³ suggested that hay fever was due to the action of the pollen protein in hypersensitive people. But it is evident that the majority of instances of the so-called idiosyncrasies which are reported in the literature have only the inference based on clinical observation to support the theory of protein sensitization, or anaphylaxis.

In 1909 Smith⁴ reported the case of a man who throughout his life had a most remarkable hypersensitiveness to buckwheat. This hypersensitiveness was first noticed when he was nine years of age. After having eaten part of a buckwheat cake urticaria, angioneurotic edema and vomiting occurred. Thereafter, whenever he ate any food containing buckwheat or went into a room where it had been handled, he experienced the same reaction.

In order to determine whether or not he was sensitive to buckwheat, certain observations were made. His arm was scarified in two places. A grain of buckwheat was rubbed into the upper scarification, while a mixture of sterile flour and water was applied to the lower one. The denuded areas were situated about three inches apart. Controls were also used. Within fifteen minutes after the vaccination the patient was conscious of a beginning reaction; he complained of a

* From the Harriet Lane Home and Department of Pediatrics, Johns Hopkins University.

1. Von Pirquet and Schick: *Die Serum Krankheit*, Leipsic, 1905.

2. Meltzer, S. J.: *Jour. Am. Med. Assn.*, 1910, iv, 1021.

3. Wolff-Eisner, A.: *Das Heufieber, sein Wesen und seine Behandlung*, München, 1906.

4. Smith, Harry Lee: *Arch. Int. Med.*, 1909, iii, 350.

tight feeling in his chest and of nausea. He began to cough at frequent intervals and there was noted increase in the respiratory movements. There were asthmatic breath sounds, marked urticaria, edema of the lips, etc. Upon removal of the dressings it was found that only the upper scarification showed any local reaction. Here there was an urticarial wheal the size and shape of a half-dollar piece. It was fully an hour and a half after the onset of symptoms before the symptoms had begun to subside. Several hours later the wheals had disappeared, but the skin surrounding the scarified points was distinctly blanched. All control tests were negative.

A series of admirable observations was conducted by Schloss⁵ on a patient who was susceptible to egg, oatmeal and almonds. When food containing any of these substances was ingested, a severe urticaria, angioneurotic edema and vomiting immediately resulted. Schloss found that these symptoms were produced by the protein alone and demonstrated by animal experiments that the condition was due to a state of hypersusceptibility to these proteins. He sensitized guinea-pigs with blood serum obtained from this patient. They succumbed later to the intravenous injection of egg white. He also rendered this patient immune by feeding him increasing amounts of egg-protein, beginning with very small amounts. Bruck⁶ was able to sensitize guinea-pigs with the serum of a patient susceptible to pork. These observations indicate that the idiosyncrasy of certain individuals to food is due to protein sensitization or anaphylaxis. Talbot⁷ reported eleven cases of idiosyncrasy to egg as determined by cutaneous tests. Six of the patients had asthma and were benefited by the withdrawal of egg from the diet. Ten of the eleven patients gave a history of having had eczema during infancy. For this reason he tested a few eczema patients with egg white, but obtained a positive reaction in only one instance. Schloss⁸ in a study of cases of food allergy, which he has recently reported, also refers to a group of patients with eczema who gave positive cutaneous reactions with various forms of food.

It is well known that many children the subjects of asthma, suffer from eczema in infancy or early childhood. Furthermore, patients with an idiosyncrasy to various foods give, with much regularity, a history of eczema in infancy. It was therefore considered of interest to determine the frequency of protein reactions in eczema, to see if a relation existed between the disease and protein sensitization and to observe the effects of variations in the protein of the food upon the course of the disease.

5. Schloss: *AM. JOUR. DIS. CHILD.*, 1912, iii, 341.

6. Bruck: *Arch. f. Dermat. u. Syph.*, 1909, xcvi, 241.

7. Talbot: *Boston Med. and Surg. Jour.*, 1914, clxxi, 708.

8. Schloss: *Trans. Am. Pediat. Soc.*, 1915, xxvii, 60.

The demonstration by Smith⁴ that the inoculation of the sensitizing substance (buckwheat) into the skin is followed by an immediate but transient urticarial wheal offered a method by which individuals could be tested for a state of hypersusceptibility to various substances. As the result of Smith's and Schloss' studies, in which the manifestations following the ingestion of buckwheat, egg, oatmeal and almonds were shown to depend on a hypersensitiveness to protein, it seems reasonable to assume that a person is sensitive to protein or that he has an idiosyncrasy to the protein of a food if an urticarial wheal develops after a protein substance or a food has been rubbed upon an abraded surface, which constitutes cutaneous test. This method was used by Smith, Schloss and Talbot. I have used this method, as well as the injection of the substance into the skin, which I designate the intracutaneous test.

In the cutaneous method the skin may be scarified with a needle or with a von Pirquet scarifier. In the tests here reported the skin was scarified with a needle and the substances used were gently rubbed in. The scarification should be superficial and blood should not be drawn. A positive reaction is shown by the appearance of an urticarial wheal or of marked erythema and edema at the point of scarification. The reaction appears within the first five minutes, increases rapidly and reaches its height in ten or fifteen minutes. It gradually subsides, but in the majority of instances the papule persists thirty minutes or more. A control should always be made as in certain individuals, especially those who are sensitive to protein substances, a slight erythema with edema may appear at the point of scarification alone. A similar reaction may take place about the substances which react negatively, but it is easily differentiated from the positive reactions. It is never so intense and disappears within ten or fifteen minutes.⁹ The difference between a negative and a positive reaction is well illustrated in Table 1.

In the intracutaneous method 0.02 c.c. of the solution is injected into the skin by means of a small tuberculin syringe and fine needle. A positive result is indicated by a reaction similar to that obtained by the cutaneous method. The erythema and the edema gradually increase and reach their height in the first ten or fifteen minutes. This reaction persists for thirty minutes or more. A reaction often occurs at the

9. In a recent article by Strickler and Goldberg (Jour. Am. Med. Assn., 1916, lxvi, 249), the statement is made that reactions are to be considered positive only when an erythema remains around the point of scarification for forty-eight hours. There does not seem to be justification for the establishment of such a criterion. With the patient of Smith application of buckwheat to the denuded surface produced a violent local reaction which persisted only for a few hours; and the patient described by Schloss, with all clinical and laboratory evidences of hypersensitiveness to several proteins, reacted locally but only temporarily.

site of the control and of the negatively reacting substance, but it is never so intense and the papule reaches its maximum diameter in five or ten minutes and gradually subsides within fifteen or twenty minutes. At times the erythema marking the site of the injection may persist in both negative and positive reactions for from twelve to twenty-four hours. The difference between negative and positive reactions are indicated in Table 2. It is advisable to observe the reactions after

TABLE 1.—EFFECT OF VARIOUS PROTEINS APPLIED BY THE CUTANEOUS METHOD ON THE PATIENT IN CASE 3

Min-ute	Distilled Water Control	Egg White	Whole Milk	Barley Water	Horse Serum
1	No Reac.	No Reac.	No Reac.	No Reac.	No Reac.
3	No Reac.	Erythema and papule 5 mm.*	Erythema and papule 5 mm.	No Reac.	No Reac.
5	Slight erythema 2 mm.	Erythema and papule 1 cm.	Erythema and papule 7 mm.	No Reac.	Erythema and papule 3 mm.
10	Erythema and papule 5 mm.*	Erythema and papule 1.5 cm.	Erythema and papule 1 cm.	No Reac.	Erythema and papule 3 mm.
15	Fading	Erythema and papule 2 cm.	Erythema and papule 1.4 cm.	No Reac.	Fading
20	Fading	Erythema and papule 2 cm.	Erythema and papule 1.5 cm.		
25	Erythema and papule 2 cm.	Erythema and papule 1.5 cm.		
30	Fading 2 cm.	Fading		
1 hr.	Definite, but less intense			
Result	Negative	Positive	Positive	Negative	Negative

* This represents the diameter of the papule

TABLE 2.—EFFECT OF VARIOUS PROTEINS APPLIED BY THE INTRACUTANEOUS METHOD ON THE PATIENT IN CASE 20

Min-ute	Dist. Water Control	Egg White	Milk	Barley Water	Horse Serum
5	Erythema and papule 5 mm.	Erythema and papule 5 mm.	Erythema and papule 4 mm.	Erythema and papule 4 mm.	Erythema and papule 5 mm.
10	Erythema and papule 5 mm.	Erythema and papule 7 mm.	Erythema and papule 7 mm.	Erythema and papule 4 mm.	Erythema and papule 5 mm.
15	Erythema and papule 5 mm.	Erythema and papule 1.2 cm.	Erythema and papule 1 cm.	Erythema and papule 4 mm.	Erythema and papule 5 mm.
20	Fading	Erythema and papule 1.5 cm.	Erythema and papule 1 cm.	Fading	Fading
25	Fading	Erythema and papule 1.5 cm.	Erythema and papule 1 cm.		
30	Gone	Erythema and papule 1.5 cm.	Erythema and papule 1 cm.		
Result	Negative	Positive	Positive	Negative	Negative

twenty-four hours as occasionally a delayed reaction occurs, that is, while at first there is no erythema or edema at the point of injection, after twelve or twenty-four hours a definite urticarial wheal develops.

It is necessary to compare the reactions of the control substances with those of the test substances in order to interpret the results correctly. As the erythema produced by each method is variable, it is more satisfactory to measure the area of induration and edema and to differentiate a negative from a positive result by this measurement. The reactions are more difficult to interpret in the intracutaneous method, as even the injection of distilled water is often followed by the development of a papule. This is much more marked in patients who are sensitive to protein, and on account of this, dilute solutions should be used for injection. As a rule the reactions are sharp and distinct and with experience the differentiation between the negative and positive reactions is not difficult.

The reaction to a number of substances was determined. Sterile water was used for the control. In the majority of instances the reaction to egg white, cow's milk and woman's milk undiluted was determined, together with ovomucoid prepared by the Mörner method and pure casein from cow's milk. These latter substances were used in a 1 to 1,000 and 1 to 100 dilutions respectively. The reaction to a 1 to 10 solution of barley flour, to undiluted horse serum and to an aqueous solution of the protein made from beef was determined in most of the cases. These substances, with the exception of egg white, were sterilized by heating to the boiling point for five minutes.

The patients who were studied may be divided into three groups: Group 1, patients without eczema, asthma or idiosyncrasy to food; Group 2, patients with eczema; Group 3, patients with skin lesions other than eczema.

In Group 1, forty-three patients were tested. They may be used as controls, inasmuch as in no one of them was there a history of eczema, asthma or idiosyncrasy to food. Twenty-seven patients were under 1 year of age, ten patients were under 10 years and six patients were between 10 and 40 years of age. A few of the infants were exclusively breast fed, but others were given both woman's and cow's milk and the majority of the patients were on a general diet. All of the forty-three patients were tested by the cutaneous method and the reactions were quite negative. Nineteen patients were tested by the intracutaneous method, and the reactions were negative in eighteen and positive in one. This infant gave a positive reaction to egg white and to ovomucoid. He was 9 weeks old and weighed eleven pounds. Since birth, he had been given woman's milk alternating with a formula of cow's milk, water and lactose. He never had had eczema and showed

no idiosyncrasy to egg when it was given by mouth. It is of interest to note that the reaction was negative by the cutaneous method. The results of the above tests are indicated in tables 3 and 4.

TABLE 3.—REACTION TO VARIOUS PROTEINS ADMINISTERED BY THE CUTANEOUS METHOD IN FORTY-THREE CASES

Reaction	Control	Egg White	Cow's Milk	Woman's Milk	Ovo-mucoid	Casein	Barley	Horse Serum	Meat Juice
Negative	0	43	43	43	43	43	43	18	20
Positive	0	0	0	0	0	0	0	0	0

TABLE 4.—REACTION TO VARIOUS PROTEINS ADMINISTERED BY THE INTRACUTANEOUS METHOD IN NINETEEN CASES

Reaction	Control	Egg White	Cow's Milk	Woman's Milk	Ovo-mucoid	Casein	Barley	Horse Serum	Meat Juice
Negative	0	18	19	19	18	19	19	19	19
Positive	0	1	0	0	1	0	0	0	0

These results demonstrate that individuals without eczema or an idiosyncrasy to food do not as a rule give a reaction when protein substances are applied directly to the skin or injected intracutaneously.

In Group 2, patients with eczema, the age of the patients varied from 5 weeks to 40 years. Eighteen were infants under 1 year of age, four were from 1 to 3 years of age, two were 6 to 12 years of age and three were from 20 to 40 years.

For convenience of description the type of eczema may be spoken of as mild and severe. In the mild cases the lesions were usually localized to the scalp and cheeks with small areas on the extremities. The distribution was more extensive in the severe cases and usually a large part of the body was involved. All types of the disease were studied—squamous, papular and vesicular; either dry or moist and with crust formation. In many of the cases there was marked induration of the skin with secondary infections. Both acute and chronic stages were studied. Urticarial lesions were present in several cases of the severe type. In all patients discomfort from itching was a marked feature.

The tests were made on twenty-seven patients. The cutaneous method was used in all, and a positive reaction was obtained in thirteen, while the reaction was negative in fourteen. Eleven patients who gave a negative reaction by this method were tested by the intracutaneous

method and a positive reaction was obtained in nine. In two patients the reactions were negative both by the intracutaneous and the cutaneous methods.

✓ The reactions were determined by the intracutaneous method in nineteen patients. A positive reaction to one or more substances occurred in seventeen, while two were negative. One of these was a boy of 6 years who had a mild eczema of a month's duration localized about the buttocks, and the other was an adult with a generalized squamous eczema and a very severe and persistent urticaria.

TABLE 5.—SUMMARY OF RESULTS

	Number of Patients	Positive	Negative
1. Cutaneous and intracutaneous methods.....	27	22	5
2. Cutaneous method	27	18	14
3. Intracutaneous method	19	17	2
4. Intracutaneous method on patients who gave negative reactions by the cutaneous method.....	11	9	2

The negative reactions by the cutaneous method were obtained in mild cases. In the severe cases the cutaneous method invariably gave reactions which were as sharply defined as those obtained by the intracutaneous method. That this latter method is more sensitive and reliable is demonstrated by the fact that nine of the patients who gave negative reactions by the cutaneous method gave positive reactions by the intracutaneous.

In order to say that the positive reactions were produced by the protein and that it was not due to other elements in the food or the result of irritation of the skin, the reactions to certain nonprotein substances were ascertained. Dilute solutions of acid and alkali, oil, sugar solution and butter fat were applied by the two methods in twelve eczema patients who reacted positively. The results were entirely negative.

The idiosyncrasy to protein as determined by the tests was not confined to a single protein, as positive reactions occurred with many different proteins. This was especially true when the intracutaneous method was used. Four patients tested only by the cutaneous method gave a positive reaction to egg white alone and one patient gave, by the cutaneous method, a positive reaction to woman's milk alone. This has also been the experience of Schloss, who found it unusual for the idiosyncrasy to be confined to one form of protein.

Egg white, woman's milk and cow's milk were the substances that most frequently caused a positive reaction. Comparatively few positive reactions were obtained with barley, horse serum and meat extract. This may be explained in part by the fact that only the cutaneous method was used in most of the tests of these substances. The number of positive and negative reactions to the different proteins is shown in Table 6.

TABLE 6.—THE NUMBER OF POSITIVE AND NEGATIVE REACTIONS TO VARIOUS PROTEINS

Substances Used	Reactions		Total
	Negative	Positive	
Sterile water (control).....	27	0	27
Egg white.....	6	21	27
Cow's milk.....	10	17	27
Cow's milk casein.....	10	17	27
Woman's milk.....	13	10	23
Ovomucoid.....	6	21	27
Barley.....	19	8	27
Horse serum.....	20	7	27
Meat extract.....	15	6	21

Only one patient gave a history of idiosyncrasy to food. In a child 13 months old there was a history of vomiting and urticaria when he was first given egg. During his stay in the hospital egg was given repeatedly by mouth without any ill effects. Only one patient showed manifestations commonly associated with protein sensitization. This was a young man, 27 years old, who invariably developed a severe attack of hay-fever whenever associated with horses.

There was no constant relation between the reactions and the diet which the patients had been taking. In one, a breast-fed infant 5 weeks old, the reaction was positive to only egg white. Three other breast-fed infants reacted positively to egg white, woman's and cow's milk.

Discomfort from the tests was infrequent. The older children and adults very often complained of slight itching about the site of the injections and in a number of patients definite urticaria-like wheals were produced in the neighborhood of the reactions. In one infant a very severe reaction was induced by the first intracutaneous injection of egg white. A severe urticaria occurred involving the entire body and after four hours the patient's temperature rose to 105. The inten-

sity of the symptoms gradually lessened after about two hours. The tests were repeated after a few days without bringing about any such symptoms.

That the reactions to protein substances are peculiar to eczema and do not commonly occur in other inflammatory conditions of the skin, is shown by the findings in Group 3. Two patients with scabies, three with generalized furunculosis and two with impetigo contagiosa gave negative reactions to egg white, cow's milk and barley water by both cutaneous and intracutaneous methods. The reactions were also negative in three patients with persistent urticaria and in one with angio-neurotic edema. These latter results were rather surprising, inasmuch as protein has been supposed to be an important factor in the production of these conditions. One patient with dermatitis herpetiformis gave a positive reaction to egg white, cow's milk and horse serum by the intracutaneous method. Schwarz¹⁰ has suggested that this disease is due to protein sensitization, although as yet there is no convincing proof of it.

The results of these observations show that twenty-two¹¹ of the twenty-seven patients with eczema gave, either by the cutaneous or intracutaneous method, a positive reaction to one or more forms of protein. Such reactions were not obtained in persons without eczema or with any regularity in patients with other skin lesions.

In order to establish, if possible, a more definite relationship between eczema and protein sensitization, a number of different experiments were undertaken. First, an attempt was made to show the presence of some substance in the serum of patients with eczema which by its action on or in combination with the proteins would produce an urticaria when injected into the skin of normal persons. Different dilutions of ovomucoid and of casein were mixed with the patient's serum and after varying periods of incubation at 36.5 C. (97.7 F.), tests were made on patients without eczema. These results were negative. They accord with those of Schloss, who was not only unable to demonstrate substances in the patient's serum which would produce an urticaria, but could not demonstrate protective substance in the patient's blood.⁵ An interesting observation was made in this connection, however, which is being further investigated. In every instance the patient's serum gave a definitely positive reaction when reintroduced into the skin of the patient.

A second series of experiments was made to determine the presence of precipitins in the blood of children with eczema. It has been demonstrated that foreign proteins are occasionally present in the blood of

10. Schwarz: Jour. Cutan. Dis., 1913, xxi, 994.

11. Patients who gave negative reactions by the cutaneous method were not retested by the intracutaneous method.

infants with marasmus (Moro¹²) and with chronic nutritional disturbances (Lust¹³). Modigliani and Benini¹⁴ found that precipitins could be demonstrated in the blood of newly born infants with diarrhea and sepsis. They did not occur in healthy, breast-fed infants even during an acute intestinal disturbance. Tests, according to the usual technic, carried out with the blood serum of four infants with severe eczema, failed to give positive precipitin reactions with cow's milk and with egg-albumin.

Finally, an attempt was made to sensitize passively guinea-pigs to egg white and to cow's milk with the serum from patients with eczema. The blood serum of three patients was injected intraperitoneally into a number of guinea-pigs. Twenty-four hours later intoxicating doses of egg white and of cow's milk were injected intraperitoneally in a few animals and directly into the heart in others. The introduction of egg white and cow's milk failed to produce any of the symptoms of anaphylaxis in these animals.

The results of these experiments were not surprising, as none of the manifestations seen in the severe cases of food allergy are present in the majority of patients with eczema and it has been Schloss'¹⁵ experience that passive sensitization can be produced only with the blood serum of patients with the most severe forms of food idiosyncrasy.

The effect of variations in the protein of the diet on the course of the eczema was observed in a number of patients. It was found early in the investigation that in order to obtain prompt results all animal protein, such as all forms of meat, eggs, milk, etc., had to be rigidly excluded. This was necessary for two reasons: In the first place, these patients give skin reactions to a large number of different proteins, so that the protein to which they are sensitive may easily be overlooked. In the second place, it was found that a patient giving a negative cutaneous reaction to a certain protein could have a systemic reaction when it was given by mouth. This is illustrated in the case of a young man with a generalized eczema of long duration, who gave a negative reaction to egg. When egg was given by mouth, however, an exacerbation of the eczema promptly occurred. Small amounts of the protein in cereals and vegetables could be taken without harmful effects.

The response to a diet poor in protein and one in which all animal protein had been excluded was striking. Improvement often began within the first two days and the condition usually subsided after three or four days. Induration of the skin and urticaria-like lesions often

12. Moro: *München. med. Wchnschr.*, 1906, liii, 2383.

13. Lust: *Jahrb. f. Kinderh.*, 1913, lxxvii, 383.

14. Modigliani and Benini: *Policlinico*, Rome, 1914, xxi, 540.

15. Schloss: *Tr. Am. Pediat. Soc.*, 1915, xxviii, 60.

persisted for a longer time. In some of the patients there was no return of the eczema, while in others recurrences were observed. The lesion during the recurrence, however, was seldom as severe as that in the original attack. A very gradual return to protein food was begun after all evidences of the disease had disappeared, and in a few cases a return to a full protein diet was accomplished without recurrence of the eczema. It is of interest in this connection that whereas the patient of Schloss had to begin with minimal doses of the protein to which he was sensitive in order to become desensitized, these patients could begin with relatively large amounts of animal proteins. Thus, one patient, after a month, was able to begin with one-half ounce of cream daily without any untoward effects. In infants this form of treatment is unsafe when continued for a long time, because a nonprotein diet cannot be substituted for cow's milk or human milk without incurring the risk of causing a severe nutritional disturbance. In older children and adults a diet low in animal protein can be continued without harm for an almost indefinite period.

This form of treatment, as illustrated by the following case reports, shows that the effect was prompt in many instances. In several patients who continued the diet for a long time permanent benefit was obtained. In a few cases no improvement was observed.

CASE 1.—M. N. (5384), boy, aged 11 months, weighing 16 pounds, had been breast fed two months, then given a mixture of cow's milk, and at 9 months of age cereals and broth had been given in addition.

Eczema began on the face when the boy was 4 weeks old. On examination there was observed a papular eruption on the extremities, and an extensive eczema of the face and scalp. The face was covered with thick crusts.

Tests were made, which gave positive reactions to cow's milk, woman's milk and egg white.

The treatment consisted of an application of lanolin to the eczematous areas. A diet was given containing cooked oatmeal, 90 gm.; butter, 10 gm., given in five feedings a day.

Thirty-six hours after the patient was given this diet a definite improvement in the condition of the eczema was noted. After four days the lesions on the face and arms were practically healed.

The child was kept on the above diet for two weeks without loss in weight, and the eczema did not return. One month later, after he had returned home and after he had received a diet of milk, eggs and cereals, the eczema was as severe as before treatment.

CASE 2.—A. T. (6950), boy, aged 16 months, weighing 19 pounds, had been taking, in addition to breast milk, cereal, bread and potatoes. The eczema began when he was 15 months old. It continued to become worse and on examination there was found a marked generalized eczema of the scalp, face and extremities.

With protein tests positive reaction to whole milk and egg white were obtained.

Lanolin was applied to eczematous areas, and a diet consisting of oatmeal, 90 gm.; butter, 10 gm., in five daily feedings was given.

After two days the lesions on the face were nearly healed. Four days after beginning treatment the eczema practically had disappeared. The skin, however,

remained irritated and discomfort was shown by the desire of the child constantly to scratch her face. The child was observed on this diet for twelve days and the eczema did not return. The weight remained stationary during treatment. The patient was seen two weeks after the special diet was discontinued and the eczema was as severe as before treatment.

CASE 3.—A. S. (6883), boy, aged 2 years, had been breast fed for two months, after which he had been given a cow's milk formula, and gradually cereal, broths and vegetables had been added to this diet. Eczema had begun when he was 1 month of age. It had rapidly involved the face and the extremities. He had been treated by many different methods and although improvement usually had been noted for a time, the condition always had recurred.

When 1 year old, he had been given a soft-boiled egg. This had been immediately vomited and he had been sick for several hours, but no urticaria had been noticed. Six months later, egg and milk had been given and he again had vomited.

As a result of the tests, positive reactions to egg, cow's milk, breast milk, barley, horse serum and beef were obtained.

The lesions were distributed everywhere over the body except the flexor surfaces of the upper and lower extremities and on the buttocks, and on the face there was a solid crust. The skin was indurated and there was a seborrheic eczema and a marked papular eczema over the rest of the body. Calomel ointment was applied to the lesions and the furuncles were incised.

The usual diet for a child of his age was given for four days, and there was practically no change in his condition. On the fifth day an oatmeal diet with butter was begun. During the next two days very marked improvement was noticed. This improvement continued, and the child after several days showed no evidences of eczema with the exception of induration of the skin. He was observed for one month and milk in small quantities was gradually added to the diet. Egg was given by mouth while the child was in the hospital, without any harmful effects. He was observed in the outpatient department, and although there were slight recurrences of the eczema on the face, the condition never became so severe as when he was first seen.

CASE 4.—J. H. (6754), girl, aged 8 years, had had the first attack of eczema when she was six years old, and after that time the disease had persisted. There was an extensive papular eczema of both cheeks, the forehead, the chest, between the shoulders, and on both arms.

Protein tests resulted in positive reactions to egg, whole milk, woman's milk, beef, barley and horse serum.

The child was given a diet of cereal with butter and vegetables. Three days after this diet was begun very marked improvement of the eczema was noticed. The child was observed in the hospital for twelve days, and the condition of the eczema never became so severe as before treatment, although there were recurrences, especially about the face.

CASE 5.—A. G. (7379), boy, aged 4 months, had been artificially fed. Eczema had begun when he was 1 month old. There was marked generalized eczema about the scalp, face, chest and extremities.

Positive reactions to egg white and woman's and cow's milk were obtained. The child was observed for two weeks and the usual local treatment for the eczema was employed, but no improvement in the eczema resulted. He was put on a diet of oatmeal 60 gm., butter 5 gm., five feedings a day, but no improvement whatever could be observed following the administration of this nonprotein diet. After ten days, because of loss of weight, it was discontinued.

CASE 7.—T. L. (34187), man, aged 26, patient referred by Dr. Thomas Brown, had had a mild eczema from time to time during his life. It had become severe enough for him to seek treatment in August, 1914. After that it had been con-

stantly present and severe. He also had had attacks of hay-fever whenever near horses. He had been treated in many ways, without relief. In the past six months he had lost 13 pounds. On examination an extensive papular and scaly eczema was found to be present, involving a large part of the patient's body, but most marked on the lower extremities.

During the first two weeks in the hospital various forms of treatment were followed by no improvement.

When the usual tests were made, positive reactions to milk, beef, horse serum and barley water were obtained.

The patient was given a diet containing no animal protein, but consisting of bread, butter, green vegetables, fruit, sugar and olive oil. During the first twenty-four hours after this diet was begun, the patient noticed that there was very much less discomfort, and for the first time in several weeks he slept well. In three days the eczema had practically disappeared. Inasmuch as there had been no cutaneous reaction to egg white, an egg was given on the fourth day. This was immediately followed by a severe exacerbation of the condition. Egg was withdrawn from the diet, and the eczema improved at once. The above diet was continued for a period of about four weeks. At the time of the patient's discharge from the hospital the eczema had disappeared except for a small patch about the toes. Later, cream and egg were begun in small amounts, and the eczema had not recurred after six months.

CASE 8.—(34405), man aged 54, had had the first attack of eczema in February, 1915, involving chiefly the lower extremities. From February to April urticaria and attacks of angioneurotic edema had occurred frequently. In April, 1915, the eczema had become generalized. On examination a papular eczema with marked desquamation was found to be present on the scalp, face, upper and lower extremities and chest.

The protein tests resulted in positive reactions to milk, beef, horse serum and barley water.

In addition to local measures he was given a nonprotein diet. After several days the itching became less intense and gradually the lesions about the face and over the body became less marked. Ten days after treatment the face was smooth, and except for some hyperemia, it appeared quite normal, and the condition of arms and trunk was much improved. The urticaria disappeared with the improvement in the eczema.

It has been impossible to prove by experimental means, such as passive sensitization, demonstration of precipitins, etc., that the cutaneous reactions in eczematous patients are of the nature of anaphylaxis. That they may be taken to indicate a form of sensitization seems justifiable from the fact that Schloss was able to sensitize guinea-pigs passively with the blood of his patient, whose cutaneous reactions were similar in all respects to those obtained with my patients. That the sensitiveness may differ greatly in degree and that it may be in some instances merely local, such as in the skin while in others it may be general as well, seems not improbable. Further studies of this type of reaction are required in order to determine its true significance.

It has also been impossible definitely to establish by experimental means a relationship between protein sensitization and eczema, though there are good reasons for believing that it may play a prominent part in the causation of the disease in some patients at least. The most important of these are the association of eczemas with known instances

of idiosyncrasy to different foods, the large number of patients with eczema who respond to cutaneous tests with proteins, and the benefit which often follows the withdrawal of protein from the diet.

A history of eczema in early life is nearly always the rule with patients who are unable to take different foods, such as eggs, shell-fish, pork, etc., on account of urticaria and edema and sometimes asthma. It is much more than a coincidence. So far as has been determined it is the protein of the food alone that is at fault. Patients without eczema very rarely give positive reactions to protein, while the proportion of those with eczema that do so is large, there being twenty-two out of my twenty-seven. It may well be that my five patients that yielded negative reactions might have yielded positive reactions if other proteins had been used. It cannot be considered that they were not susceptible to any protein. Finally, the evidence afforded by those patients that respond promptly and permanently to the withdrawal of some or all of the animal proteins from the food is very strong. The number is not large, but the results are striking.

SUMMARY

Of forty-three patients without eczema, only one showed any evidence of susceptibility to protein by cutaneous and intracutaneous tests.

Of twenty-seven patients with eczema, twenty-two gave evidence of susceptibility to proteins. Egg white, cow's milk and woman's milk were the substances that most frequently caused a reaction. If there was a reaction from one protein there usually was a reaction from several.

The intracutaneous test is more delicate than the cutaneous, but gives results that are more difficult to interpret.

The removal of some or all of the animal proteins from the food brings about great improvement in some cases of eczema in older children and adults. With infants it is not successful, first, because it is impossible to feed an infant for a long time upon a diet that contains no animal protein, without the risk of seriously affecting his nutrition, and second, because there is a strong tendency for the eczema to return, even though a protein-poor diet produces early improvement, and even though the protein-poor diet is continued.

CLINICAL DEPARTMENT

REPORT OF A CASE OF NONPARASITIC CHYLURIA, CHRONIC NEPHRITIS, IN A CHILD

WITH NECROPSY

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Nonparasitic chyluria is a rare affection in adults and exceedingly rare in children. While most of these cases are due to a lymphangiectasis and a consequent rupture of the lymphatics in the pelvis of the kidney or in the bladder, the etiology of this disease is nevertheless somewhat uncertain.

Jennie G. was admitted to the Beth Israel Hospital on Jan. 1, 1916, when eight years old. Her parents and their four other children were alive and well.

The child had been nursed until 1 year of age. She had suffered from a chronic cough from the eleventh month until the end of the second year, when she had a severe attack of measles. During the fourth year it had been noticed that the child's abdomen became enormously enlarged and that she steadily lost weight. The parents consulted a number of physicians, including the writer. At that time, having found ascites in the puny, undersized child, with a history of cough of long standing, normal urine and no abdominal tumor, I suspected tuberculous peritonitis, although the temperature was normal and the von Pirquet test was negative. The parents would not permit tapping of the abdomen. On prolonged use of tonics with creosote, together with good nourishment, the child gained weight, and in the course of eighteen months the ascites almost disappeared.

In the month of May, 1914, the child had been brought to me, and the mother had told me that for the previous two months the patient had again been losing weight, had had frequent micturition and the urine had been milky in appearance. She was very anemic, weighed only 28 pounds and some dulness could be detected at the lower part of the abdomen. The urine looked turbid, and fibrinous coagula were observed when it had stood for some time. By shaking the urine with ether, the dissolved fat rose to the surface and the urine became quite clear. Microscopically, the fat globules were in a fine state of subdivision. Sudan III stained the fat particles red. No filaria and no blood had been detected. By advising complete rest, involving the absence from school, and the administration of salol, urotropin and belladonna, there was slow improvement, some weight was gained and on July 31, 1915, the urine was examined by Dr. Max Kahn who reported that it contained a huge amount of mucin, but no lactose, fat or casein.

On Nov. 27, 1915, the frequent micturition and milky urine reappeared. Dr. D. Constantinides examined the urine and found albumin 0.365 per cent., fat 0.225 per cent., sugar negative; also some pus cells and epithelium. On allowing the urine to stand, a creamlike mass of fat rose to the surface.

Condition on Admission.—The child was anemic and very emaciated, weighed only 34 pounds, was not playful, complained of frequent frontal headache, was nauseated and vomited several times a day, was very thirsty, with general

weakness, constipation and loss of appetite. The heart, lungs and abdominal organs were normal; there was some dulness at the lower part of the abdomen and some nodules could be palpated at the right inguinal region. The glands at both groins were also palpable. There was no edema and no cyanosis. The patella reflexes were somewhat exaggerated. The temperature was 99.4, pulse 120, respiration 28.

A blood examination showed erythrocytes 3,800,000, total leukocytes 14,400, polymorphonuclear cells 70 per cent., lymphocytes 30 per cent. There was no eosinophilia. The hemoglobin was 60 per cent. No filaria were found in the blood.

Von Pirquet tests were done twice with negative results; Wassermann test was also negative. The stools contained no ova or red cells. The guaiac test for sugar was positive.

REPORT OF URINE EXAMINATION BY DR. D. CONSTANTINIDES

Amount in 24 hours.....	500 to 600 c.c.
Appearance	Somewhat milky
Specific gravity	1.012
Albumin	0.6 per cent.
Sugar	Negative
Urea	0.625 per cent.
Total nitrogen	0.42 per cent.
Chlorids	0.38 per cent.

Extract after evaporation—

Solids	22.8 gm. in 1,000 c.c.
Organic matter	18.3 gm. in 1,000 c.c.
Inorganic matter	4.5 gm. in 1,000 c.c.
Fat	1.5 gm. in 1,000 c.c.

The urine also contained lecithin and cholesterin.

The microscopic examination showed many white cells, a few hyaline casts and bladder epithelium, but no filaria. A diagnosis was made of chyluria.

During the first week of the child's stay in the hospital, under the administration of urotropin and sodium benzoate her condition improved somewhat and at times the urine almost cleared up, but it always contained some fat. Then the temperature began to rise and reached as high as 104.6. The headache, nausea and anorexia increased in severity, the urine became loaded with pus, markedly ammoniacal, and the fat increased in quantity. The stools contained some blood. The cervical glands became enlarged, although there was no congestion of the throat, and some ecchymotic spots were noticed all over the body and extremities. The pulse became very weak and at times irregular.

The eyes were examined by Dr. Ervin Török on January 15 and he found that the pupils reacted only sluggishly to light. The whole of both disks was covered with a whitish exudate and was moderately swollen. There were several hemorrhages on and around the disks. The blood vessels were large and tortuous. The diagnosis was albuminuric retinitis.

A blood culture gave a negative result. The same evening and on the following day the patient had a number of convulsive attacks, which were most marked on the right side of the body. These were controlled by chloroform. A lumbar puncture was done, but the spinal fluid was normal.

On January 17 the patient became comatose and the pulse was at times imperceptible. The cervical glands became more enlarged and death ensued from cardiac failure.

Postmortem and microscopic examination was performed by Dr. Eli Moschowitz, pathologist to the Beth Israel Hospital, to whom I am indebted for the following report:

A necropsy was performed on the child Jennie G. (Case 6690) eight hours after death. The body was very much emaciated. The cervical, axillary and groin glands were enlarged. Some ecchymotic and petechial spots were noticed over the body and extremities. The lungs were normal, except some slight congestion. The heart was much enlarged, the muscle of left ventricle being about $2\frac{1}{2}$ cm. thick, firm and pale. The left ventricle was dilated, and the muscle of right ventricle was 1 cm. thick. The valves were normal, with the exception of a few atheromatous patches on the ventricular surface of the mitral valve. The liver was slightly enlarged and on section was of a pale, brownish red and cloudy. The stomach mucosa was covered with mucus, but otherwise normal. The right kidney was 8 by 3 by 2 cm. It was very irregular in contour, showed fetal lobulations, and was fairly firm, with the capsule adherent. The surface beneath was very irregular, with numerous depressions and sulci between prominences seeming to represent remnants of kidney tissue. These prominences were paler than the surrounding portions, project above the surface and, on section, were grayish and sharply defined from the surrounding tissue. Section through the kidney proper showed a complete obliteration of all markings, so that it was impossible to differentiate cortex from medulla. The cut section was pale red. There were numerous ecchymoses on the surface, the pelvis was somewhat dilated, and the papillae were flattened. The ureter was somewhat dilated and thickened. The left kidney was 6 by 3 by 2 cm., was somewhat smaller than the right and presented practically the same picture, except for the absence of fetal lobulations. Only the left adrenal was removed; it was slightly enlarged, otherwise normal. The pancreas was enlarged. The spleen was also enlarged and measured $12\frac{1}{2}$ by 6 by 3 cm. The surface was smooth. It was deep red on section and the pulp was firm. The malpighian bodies were prominent. There was a fresh infarct of a dirty brown color, about the size of a bean in the lower pole, soft in texture and sharply circumscribed from surrounding tissue. The intestines were normal, the mesenteric lymph nodes enlarged. The bladder was dilated, the walls being extremely hypertrophied, the mucosa smooth, and presenting many ecchymotic areas.

An anatomical diagnosis was made of chyluria; chronic diffuse nephritis (contracted kidney); chronic congestion of lungs; hypertrophy and dilatation of left ventricle; splenic hyperplasia with fresh infarct; parenchymatous degeneration of liver; hypertrophy and dilatation of bladder; hypertrophy and dilatation of ureters.

Microscopic examination of the lungs showed the epithelium of the bronchi to be desquamated and the lumen to contain an exudate of polymorphonuclear cells. Around the smaller bronchi the alveoli contained an exudate consisting of polymorphonuclears and round cells. The walls of the alveoli in the remainder of lung were thickened and the capillaries were markedly dilated. The muscular fibers of the heart were normal and there was no infiltration. The cells of the liver were slightly granular, and the nuclei somewhat pale. There was a very moderate amount of fat in the cells.

Examination of the spleen showed the splenic veins to be dilated and filled with blood. An infarct showed profound necrosis. There were many shadow cells and nuclear detritus: Some of the blood vessels in the necrosed area were still preserved and contained red thrombi; others showed beginning hyaline degeneration. The splenic veins surrounding the infarct were dilated to an enormous size. The capsule and trabeculae of the spleen were normal.

The pancreas showed a few areas of autodigestion. Scattered here and there throughout the organ were small focal areas of polymorphonuclear infiltrations. In these areas the pancreatic cells stained less deeply than in the remainder of the organ. The islands of Langerhans were normal.

The microscopic picture of the kidneys, even on superficial inspection, was seen to be completely disorganized. The interstitial connective tissue was enormously increased and in areas showed a profound infiltration with round and plasma cells. The tubules varied greatly in size and in shape; no distinction could

be made between any of the various portions of the tubules. The majority of the tubules were dilated, the epithelium was flat and stained poorly. Most of them contain hyaline casts, and some of these casts contained polymorphonuclears. The glomeruli revealed various forms, some being completely hyaline, some partially so; some containing new connective tissue, others enormously hypertrophied, and still others showing a polymorphonuclear infiltration. The Bowman capsules were uniformly intact. A few of the glomeruli contained bacterial thrombi. The capillaries were very prominent and dilated.

In the adrenals the cortical cells did not stain uniformly, some being extremely pale. Just beneath the capsule were many small foci of polymorphonuclear infiltrations. In the center of the majority of these foci were small bacterial emboli. There were a few bacterial emboli just beneath the capsule that were not surrounded by polymorphonuclear infiltration. The capsule of the adrenal showed marked extravasation of blood. The medullary portion of the adrenal revealed nothing abnormal.

The intestines and the mesenteric lymph nodes were normal. In the submucous connective tissue of the bladder there was a marked blood extravasation, but the organ was otherwise normal.

REMARKS

This case presents a number of interesting features:

1. It is possible that the severe attack of measles at the beginning of the third year was the causative factor of the kidney derangement and also the cause of the chyluria. While a serious degree of nephritis is supposed to be rare after measles, still Dr. E. Henoch states that as in other infectious diseases, cloudy swelling of the cortex of the kidney is by no means infrequent. Dr. Henoch met with three cases and Dr. G. F. Still saw two cases of nephritis following measles.

2. Had the parents allowed us to tap the abdomen when the ascites was most marked, we probably would have found chylous fluid.

3. There was a disappearance of the ascites under tonic treatment and a marked improvement of the chyluria by rest and the administration of urotropin, salol and belladonna.

4. The course of the disease during the last few days before death and the necropsy findings certainly point to chronic diffuse nephritis, chyluria and some general septic infection. Still, the blood culture failed to show any organisms.

Chyluria (nonparasitic), as already stated, is excessively rare in childhood and a survey of the literature fails to locate any special article which considers it at this period of life. Of five patients who might be classed as children, two were 16, one was 15 and in another no age is mentioned, the patient being termed "a young girl," who was doubtless at least in her teens. The remaining case occurred in a child of 18 months and it is not known that chyluria existed for more than a single day.

It is therefore highly probable that the author's case is almost if not quite unique, at least as far as age incidence is concerned. Four of

the patients might be ranked as adults and the remaining patient as an infant.

A few words concerning these cases may be of interest. The case¹ in the infant was one of combined chyluria and glycosuria, such as has been encountered at times in adults. There is said to have been familial diabetes in the families of both parents. The attack of glycosuria lasted several days and could not be traced to the ingesta. As already stated, the urine was milky on one day only and only the forenoon urine.

Bouchut² saw chyluria of a week's duration in a very hysterical girl of 15. The urine separated into two strata on standing, the upper one thick and creamlike, the lower shallow and clear.

Pasteau's³ case in the "young girl" was associated with right nephroptosis and left renal tuberculosis. Chyluria was most marked in the night urine.

Phillips'⁴ case in a boy of 16; chyluria appeared after recumbency, whether at night or in the daytime.

Becigneul's⁵ case was much like the preceding, occurring in a 16-year-old boy and only upon passing urine after recumbency. The condition was intermittent and lasted eight months.

In none of the above cases was any parasite found.

50 East Ninety-Sixth Street.

1. Brandenburg: *Deutsch. med. Wchnschr.*, 1909, xxxv, 934.

2. Bouchut: *Gaz. d. hôp.*, 1879, No. 36, lii, 874.

3. Pasteau: *Asso. française d'urologie*, 1908, xii, 256.

4. Phillips: *Tr. Clin. Soc.*, London, 1898-1899, xxxii, 216.

5. Becigneul: *Gaz. med. de Nantes*, 1903, Series 2, 403, 405.

SKIN MANIFESTATIONS WITH STREPTOCOCCUS INFECTION

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The following clinical history is that of a child, who, during an attack of bronchopneumonia, developed a generalized streptococcic infection. This was exhibited clinically by the almost simultaneous appearance of a purulent arthritis, erythema nodosum and erysipelas. A streptococcus was cultivated from the blood, from a joint effusion, and from an excised nodule.

A suspension of the organism from these three sources was injected intravenously into three rabbits. Those receiving the bacterial growth obtained from the excised node and from the joint effusion died within forty-eight hours from septicemia. The rabbit which received the streptococcus isolated from the patient's blood was killed on the fifth day after injection. The right ankle joint was swollen and contained purulent fluid. Cultures from this joint gave a streptococcus.

CLINICAL CASE HISTORY

E. O., boy, 17 months old, was admitted to the Children's Memorial Hospital, service of Dr. F. S. Churchill, Dec. 27, 1915. The child had been sick a week with cough, fever and vomiting. On examination it presented the usual picture of a bronchopneumonia. The tonsils were moderately enlarged and reddened, and the posterior pharyngeal wall was covered with a mucopurulent secretion. The white blood count was 20,000. The differential count showed 83 per cent. polymorphonuclears, 4 per cent. small mononuclears, 12 per cent. large mononuclears, and 1 per cent. eosinophils. Urinalysis was negative. Roentgenogram of the chest showed numerous areas of mottling over both lungs.

On Jan. 5, 1916, the patient appeared brighter. Examination of the lungs showed practically normal breath sounds, accompanied by a few scattered, crackling râles. A few days later the patient was worse. On Jan. 9, 1916, the right upper lobe disclosed new signs of consolidation. There was a double otitis media and the throat looked injected. A smear from the ear discharge exhibited diphtheroid organisms, and a throat culture gave a pure growth of these organisms. Notwithstanding the absence of clinical signs of diphtheria, 3,000 units of antitoxin were given, but the child's condition gradually grew worse.

In January 16 a triangular area of indurated redness was noted over the forehead, extending to the bridge of the nose. This area was sharply defined from the surrounding skin. The temperature fluctuated between 100 and 102.5. Almost coincident with the development of the erysipelatosus area the left knee became swollen. There was edema of both feet, and small subcutaneous nodules formed over the extensor surfaces of the legs. They were firm, oval, painful and of a pink color. Later their color changed, so that they resembled contusions. Similar nodules were present, to a lesser degree, on the forearms, and

over the anterior surface of the chest there were fine pin point petechiae. Aspiration of the knee brought a few drams of pale green pus.

Cultures were taken from the blood, from this pus and from an excised subcutaneous nodule. These were grown in tall tubes of dextrose ascites bouillon and agar. A pure culture of hemolytic streptococcus was obtained.

The child died on Jan. 19, 1916. At necropsy the anatomical diagnosis was bronchopneumonia, ileocolitis, cystitis, fatty infiltration of liver, toxic splenitis, erythema nodosum, arthritis.

Though the occurrence of erythema nodosum in association with generalized bacterial infections has long been known, bacteriologic investigation has given conflicting results. Recently, Rosenow¹ isolated from patients with erythema nodosum a diphtheroid bacillus, which closely resembled in some stages the streptococcus group, the injection of which into animals produced erythema nodosum.

Frankel² has called attention to the striking polymorphous manifestations that skin lesions assume in bacterial infections. The staphylococcus or streptococcus is the most frequent offending organism.

1. Rosenow, E.: Etiology and Production of Erythema Nodosum, Jour. Infect. Dis., 1915, xvi, 367.

2. Frankel, E.: Ueber metastatische dermatosen bei akuten bakteriellen allgemeinerkrankungen, Ztschr. f. Hyg. u. Infektionskrankh., 1914, lxxvi, 133.

A CASE OF ACUTE MYELOGENOUS LEUKEMIA IN AN INFANT *

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The case here reported as being of unusual interest is that of a girl, infant L. F., Hebrew, nine months of age, who was admitted to the Thomas Wilson Sanitarium, July 11, 1913.

Family History.—The father and mother were both well, aged 36 and 33 years, respectively. They had lost four other children in infancy, one from scarlet fever and three from "summer complaint." The patient was the only living child. There was no history of syphilis or of tuberculosis. The parents were apparently in comfortable circumstances and the hygienic condition of their home was described as "good."

Past History.—The patient's birth was normal, weight 7½ pounds. She was exclusively breast fed for six months, and for the last three months a whole milk mixture had been used as a supplementary feeding. The patient had never been ill before and had gained steadily.

Present Illness.—The baby is said to have "caught cold" two weeks previously. She was better, however, and the acute symptoms of the present condition began suddenly and without prodromata only five days before admission. These symptoms consisted principally of nausea and vomiting almost immediately after taking food, with frequent writtings between feedings. Shortly after the onset diarrhea of moderate severity began, the stools being described as fecal, fluid and mucus, but with no blood, five to eight in twenty-four hours. There was moderate continuous fever and a cough that had persisted for two weeks.

Physical Examination.—This was unimportant for the most part. Patient was fairly well nourished, somewhat pale and exceedingly fretful, weight 15¾ pounds. The throat was clear and the lungs were negative excepting for a few moist scattered râles. The heart sounds were clear. The abdomen was soft, very slightly diffusely tender and there was no enlargement of spleen. The edge of the liver was palpable. There was no general glandular enlargement; the reflexes were active and the skin clear. The temperature on admission was 102 F. The most prominent symptom during observation was almost constant nausea and vomiting after taking food; it was not forceful in character. Wretching persisted if the patient was aroused during starvation, after breast milk as well as after various cows' milk and cereal mixtures. The temperature remained continuously above 100 F., and in the last four or five days frequently reached 103 F., and once 105 F. The von Pirquet reaction was negative. The ear drums were smooth and glistening. The vomiting continued to be the dominating symptom. The stools were fecal in character and not more than three to five in twenty-four hours. The child lost continually in weight, was irritable when disturbed but not stuporous. There was little change in her condition for ten days. At that time her condition became decidedly more

* Read at the Twenty-Seventh Session of the American Pediatric Society, Lakewood, N. J., May, 1915.

serious. The vomitus developed a fecal odor. The stools at this time were four in twenty-four hours, and fecal in character. There were no other symptoms suggesting intestinal obstruction. The patient became progressively worse. A leukocyte count made at this time showed a great increase in white cells, which numbered nearly 200,000 per cubic millimeter. Smears were made, but were not studied for several days. The patient, twelve days after admission had a number of convulsive seizures ending in coma and death. Necropsy was refused.

The exciting cause of the vomiting was not determined during life. The symptoms seemed to point to gastro-intestinal intoxication with unusual gastric irritability. The differential count of the leukocytes showed the presence of a large number of myelocytes from the bone marrow and suggested the diagnosis of acute myelogenous leukemia.

The report of Dr. W. A. Baetjer of the Clinical Laboratory of the Johns Hopkins Hospital, to whom the specimen was referred, is as follows:

Leukocytes 200,000; differential count, Wilson stain, 500 cells:

	Per Cent.		Per Cent.
Polymorphonuclear neutrophils...	47.	Myelocytes—	
Polymorphonuclear eosinophils...	4.2	Neutrophils	18.
Polymorphonuclear basophils.....	0.	Eosinophils	1.6
Lymphocytes	28.6	Basophils	0.2
Large mononuclears.....	0.	Myeloblasts	0.4
Transitionals	0.	Neucleated red blood cells.....	0.

Blood Picture.—Moderate secondary anemia; no marked reduction in number of red blood cells; very few nucleated reds. Platelets about normal; no striking fragility of the cells. Polymorphonuclear neutrophils young, often with scanty granulations. The lymphocytes are mostly of the typical small variety; there are, however, a fair number of larger forms with deep basic protoplasm.

Picture resembles chronic myeloid leukemia, except for the predominance of atypical granulations in most of the myelocytes and in the high percentage of small lymphocytes, probably due to the age of the patient (9 months).

Diagnosis.—Acute myeloid leukemia; type, clinically acute. Blood picture resembling chronic myeloid leukemia with high percentage of lymphocytes due to age.

It is not the object of this report to enter upon any discussion of myeloid leukemia as a pathologic process, but simply to place this case on record as the youngest case we have been able to find in which the blood picture was characteristic. The youngest patient in a series of sixty cases of myeloid leukemia reported by Naegoli was four years.

Besides the extreme youth of the patient, the rapid course of the disease, less than three weeks, is noteworthy. There was no enlargement of the lymphatic glands or of the spleen and no evidence of hemorrhage or of necrosis of the mucous membranes. The symptoms apparently were referable to the gastro-intestinal tract. The great number of leukocytes in the circulating blood, 200,000 per c.mm. was too many to be accounted for by a possible focus of infection and directed attention to a further study of the blood. While it is possible to have perhaps as high as 15 per cent. of myelocytes in acute infections, these cells are of the typically neutrophilic variety. In this case,

however, the atypical granulations seen in the neutrophilic myelocytes, as well as the presence of eosinophilic and basophilic varieties, is good evidence of primary disease of the blood-forming organs.

From the standpoint of diagnosis, this case is of value, in that it indicates that an examination of the blood may shed light in certain instances, in infancy, of excessive nausea and vomiting, not otherwise explained.

PROGRESS IN PEDIATRICS

REVIEW ON DISEASES OF THE NEWLY BORN

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PHYSIOLOGY OF THE STOMACH OF THE NEW-BORN: THE TONUS AND HUNGER CONTRACTIONS OF THE STOMACH OF THE NEW-BORN

Carlson and Ginsburg¹ show tracings of their observations on a number of new-born infants with the results showing that the empty stomach at birth exhibits the typical periods of tonus and hunger contractions of the adult, the difference between the infant and the adult being the greater frequency and the relatively greater vigor of these periods in the young. Observations were made in some of the infants before the first nursing and it becomes clear that the gastric hunger mechanism is complete physiologically and is probably active some time before birth. They come to the conclusions that the periods of gastric tonus and hunger contractions are in evidence shortly after birth and before any food has entered the stomach. When the gastric hunger contractions become very vigorous the sleeping infant may show some restlessness and even wake up crying. If the infant is awake the very vigorous hunger contractions frequently induce crying and restlessness. The writers call attention to the fact in two of the tracings the gastric hunger periods end in incomplete tetanus which is an index of youth and vigorous stomach.

FETAL ERYTHROBLASTOSIS: FETAL ERYTHROBLASTOMATOSIS

Woolley² reviews the causes of congenital general edema in the new-born. Woolley says that in its characteristic form congenital general edema is evident at birth and appears to develop during the period in the uterus. Concerning the cause of this condition something is known of some cases, but nothing of others. He groups the causes as follows: (1) Disturbance in the portal circulation; fetal peritonitis; absence of the ductus venosus Arantii and in certain anomalies of the intestinal tract; (2) anomalies of the heart, of the vessels and of the uropoietic system of the fetus; (3) associated with maternal disease, chiefly nephritis; (4) some metabolic anomaly of the fetus develops which finds expression in abnormal blood production and edema.

1. Carlson, C. J., and Ginsburg: *Am. Jour. Physiol.*, 1915, xxxviii, 29.

2. Woolley, Paul G.: *Jour. Lab. Clin. Med.*, February, 1916, i, 347.

Woolley regards this last group as the most interesting, for in it belong the cases which have been called fetal erythroblastosis. Schridde characterizes the condition as follows: (1) The fetuses, premature, as a rule show universal edema. (2) Most of them show also edema of the placenta and cord. (3) The liver and spleen are markedly enlarged. (4) Microscopic examination of the liver and spleen show unusually large number of erythroblasts with large number of other myeloid cells inside and outside vessels. The liver cells are atrophic and in the spleen the follicles are absent. In other organs extramedullary erythroblastic nodules appear. Mitotic and rhectic figures appear and the liver cells and pulp cells of the spleen are colored with iron-containing pigment. These characteristics Woolley says were shown in their entirety in a case that he had access to. This case was more than usually interesting in that the anasarcaous fetus was one of a pair of twins. The other twin was apparently normal. Schridde believed that this fetal disease was a result of a severe fetal anemia and the anemia it was assumed was of toxic origin. Schridde did not believe it to be syphilitic.

In one of Schridde's cases the mother was nephritic, and in this instance he believed that the fetal condition was coincidental, and not the result of the maternal condition. It is generally supposed that this disease is of toxic origin and that the toxic materials, while causing destruction of the erythrocytes, at the same time stimulate the blood-forming tissue. The origin of the poisons is not known. However, the poisons certainly do not come from the maternal blood.

Woolley says that the anasarca is the expression of the anemia, which in turn is due to the disturbed production, and perhaps also to increased destruction, of erythrocytes. When anatomic defects occur in the body, anasarca also occurs, because the blood, capable though it may be, is not properly oxygenated for obvious reasons.

Woolley suggests that there is something of an analogy between this condition and leukemia, and if this conception has any force, then erythroblastosis may be looked upon also as belonging to a group of tumors. In this case it is the erythroblastic tissue which is involved.

SCLEREMA NEONATORUM

Paterson³ takes up the conflicting views of this disease, which is one of comparative rarity. He writes an interesting historical survey from the first recorded case in 1718 up to the present time. He calls attention to the early errors in the description of the disease.

Paterson says that this disease is most likely to be found where there are general conditions inimical to health. There is no direct proof

3. Paterson, W. S.: *Quar. Jour. Med.*, 1915, viii, 317.

that syphilis plays any part in the causation of this condition. Paterson thinks that the reason this disease has not been known more extensively and described more carefully is from the fact that the disease is so soon fatal, usually in poverty stricken and squalid surroundings, that the disease is not recognized, but is often ascribed to other obvious disabilities. He quotes freely from Parrot and gives him the credit for differentiating clearly the two conditions, sclerema and edema of the new-born.

Finkelstein says that in some cases this condition of sclerema and edema may be associated together. Paterson thinks that the serous infiltration is not an essential feature of the sclerema, but only a secondary sign. Paterson takes Ballantyne's definition of the disease as reasonable, that it is "a rare disease occurring in the new-born, characterized by induration of the subcutaneous tissue and little amenable to treatment." Mensi has reported on eighty-two such cases and he divides sclerema into two types, the first occurring in premature and new-born infants and in the cold season of the year. It follows a previous edema. The induration appears first in the buttocks, never or seldom in the hands and feet. It spreads more or less over the body. The temperature is usually low, seldom febrile and the disease usually ends fatally. Autopsy shows that the skin is atrophied with absence of the granular layer and the cells of the cutis are closely packed together. There was dilatation of the vessels with hemorrhage into the cutis. The second type that Mensi describes is characterized by condensation, thinning and drying of the skin. It occurs less often in premature children but mostly in warm weather and it may begin with edema. On examination postmortem there was found to be atrophy of the dermis, condensation of the fibers, scantiness of the cells and vessels of the skin and abnormal development of fibrous tissue around the fat. Paterson thinks that the large number of cases which Mensi claims to have seen raises some doubts whether they were all true cases of sclerema neonatorum.

The temperature shows some very striking records, Henock reporting one temperature of 83.3 F. and Roger one of 72 F., yet depression of the temperature is not an infallible sign. Considerable variation in the color of the skin appears, yet nothing is characteristic. In the differential diagnosis the condition of edema neonatorum is the most important disease to be differentiated from it. Edema neonatorum Paterson regards as a sign of a disease rather than a definite self-existing condition. Edema neonatorum is found usually, if not invariably, with other recognizable affections, and its distribution is as one would expect to find it, in those situations where the influence of gravity would be most favorable to its appearance. In edema neonatorum

pitting on pressure always occurs, though it is possible that in extreme cases the infiltration may be so firm that no pitting can occur, while in sclerema neonatorum there is no true pitting. Paterson says that he believes sclerema neonatorum to be a well-defined disease, not necessarily associated with or secondary to any recognizable morbid condition. It may present conditions varying widely in degree as to the extent of the local lesions and the severity of the constitutional symptoms and therefore the gravity of the ultimate prognosis.

He reports a case which he had personal observation of, a child born of healthy parents after a normal, quick labor. Thirteen hours after birth the nurse noticed that the child's face was of a dark, bluish color. This cyanosis soon passed off, but recurred in the afternoon five or six hours later. The following night these attacks came on more frequently and more violently. Each attack began with screams, the hands became rigid and fingers clenched, with marked cyanosis of the face. Each seizure lasted about ten minutes. Paterson said he could not detect any cardiac abnormality in this patient. In the morning after the birth of the child Paterson noticed that the buttocks and dorsal region had a rubber-like consistency. There was no pitting even on firm pressure and the skin could not be picked up from the underlying tissue, and even when freely handled did not appear to cause the child any pain. When it was first noticed this firmness was limited to the buttocks and the legs below the knees. Within seventy-two hours after birth the induration was found over the dorsal and lumbar regions, also about the shoulders, face and jaws, with patches over the front of the abdomen and the lateral and costal regions.

During the first week the child was extremely ill and was nourished with difficulty; but after the sixth day the stiffness left the facial muscles and the child became able to swallow. After this stiffness of the face left, it gradually faded away from the thorax and the abdomen, then from the dorsal region and lastly from the outer aspect of the thighs. This process of gradual resolution occupied fourteen or fifteen weeks. Two years after this child was born it was seen again by Paterson and it was found that the child was not in normal condition. It had a reasonably intelligent facial expression, but could not walk or even stand alone and showed an ataxic movement of the feet. There were no signs of rickets, but Paterson felt that the condition in general was suggestive of some cerebellar lesion. The second case that Paterson saw was an illegitimate child born in miserable surroundings with well-marked congenital syphilis. On the thirteenth day after the baby was born it developed a well-marked and extensive rubber hardness over the face and chest, clearly marked on the buttocks, thighs and calves. The child rapidly went to pieces and died when fourteen days old. Sections of the skin in this case do not show any increase of the

fibrous tissue, but there is a well-marked thickening of the rete malpighii.

Paterson goes into the morbid anatomy of this condition, but does not come to any definite conclusions about it because of the marked variations that the different physicians report, and in the etiology Paterson finds no satisfactory explanation of the condition.

The prognosis is always guarded, usually grave, but not invariably hopeless, and it depends to some extent on the local lesions and the presence or absence of complications. The general circumstances of the case will have much to do with the ultimate outcome.

The treatment is mostly symptomatic and nothing is as yet known to be specific for the condition.

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